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☐ 1. Document ID: US 6346248 B1

L4: Entry 1 of 2 File: USPT Feb 12, 2002

US-PAT-NO: 6346248
DOCUMENT-IDENTIFIER: US 6346248 B1

TITLE: Methods of treating autoimmune diseases with a CD86-specific immunotoxin

DATE-ISSUED: February 12, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
De Boer; Mark	Heemskerk			NLX
De Gast; G. C.	Utrecht			NLX

US-CL-CURRENT: 424/181.1; 424/130.1, 424/133.1, 424/135.1, 424/141.1, 424/143.1, 424/144.1, 424/153.1, 424/173.1, 424/178.1, 424/183.1, 530/387.1, 530/387.3, 530/388.1, 530/388.2, 530/388.22, 530/388.7, 530/388.73, 530/391.1, 530/391.7

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

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☐ 2. Document ID: US 6071519 A

L4: Entry 2 of 2 File: USPT Jun 6, 2000

US-PAT-NO: 6071519
DOCUMENT-IDENTIFIER: US 6071519 A

TITLE: Immunotoxins specific for CD86 expressing cells

DATE-ISSUED: June 6, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
De Boer; Mark	Heemskerk			NLX
De Gast; Gijsberi	Utrecht			NLX

US-CL-CURRENT: 424/183.1; 424/130.1, 424/133.1, 424/134.1, 424/135.1, 424/141.1, 424/143.1, 424/144.1, 424/153.1, 424/173.1, 424/178.1, 424/192.1, 435/328, 435/343, 435/343.1, 530/387.1, 530/387.3, 530/388.2, 530/388.22 , 530/388.7, 530/388.73, 530/391.1, 530/391.7

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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TRANSPLANTABLE.USPT,PGPB.	1058
TRANSPLANTABLE-MOUSE.USPT,PGPB.	2
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L4	L3.clm.	2	L4
L3	('B7-2' or cd86) same (antibod$) same (humaniz$ or humanis$ or chimeric or chimaeric)	15	L3
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L1	c0-man sung $	0	L1

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L5: Entry 11 of 14 File: USPT Aug 24, 1999

DOCUMENT-IDENTIFIER: US 5942607 A
TITLE: B7-2: a CTLA4/CD28 ligand

Brief Summary Paragraph Right (10):
The invention also provides methods for inducing tolerance in a subject by, for example, blocking the functional interaction of the novel B lymphocyte antigens of the invention, e.g., B7-2 and B7-3 , to their natural ligand(s) on T cells or other immune system cells, to thereby block co-stimulation through the receptor-ligand pair. In one embodiment, molecules that can be used to block the interaction of the human B7-2 antigen to its natural ligands (e.g., CTLA4 and CD28) include soluble B7-2 , antibodies that block the binding of B7-2 to its ligands and fail to deliver a co-stimulatory signal (so called "blocking antibodies") and B7-2 -Ig fusion proteins, which can be produced in accordance with the teaching of the present invention. Inducing tolerance in a subject in accordance with the methods described herein may be useful prophylactically, in preventing immune disorders such as trasplantation rejection (solid organ and bone marrow) and graft versus host disease, especially in autologous bone marrow transplantation. The methods of the invention may also be useful therapeutically, in the treatment of autoimmune diseases, transplantation rejection, and established graft versus host disease in a subject.

Detailed Description Paragraph Right (23):
Novel B lymphocyte activation antigen nucleic acid sequences from other species, such as the mouse, can be used to generate either transgenic animals or "knock out" animals which, in turn, are useful in the development and screening of therapeutically useful reagents. For example, murine cDNA or an appropriate sequence thereof can be used to clone for genomic B7-2 in accordance with established techniques and the genomic sequences used to generate transgenic animals that over-express B7-2. Methods for generating transgenic animals, particularly animals such as mice, have become conventional in the art and are described, for example, in U.S. Pat. Nos. 4,736,866 and 4,870,009. Typically, particular cells would be targeted for B7-2 transgene incorporation with tissue specific enhancers, which could lead to enhanced T cell proliferation and autoimmunity. Transgenic animals that include a copy of a B7-2 transgene introduced into the germ line of the animal at an embryonic stage can be used to examine the effect of increased B7 expression. Such animals can be used as tester animals for reagents thought to confer protection from, for example, autoimmune disease. In accordance with this facet of the invention, an animal is treated with the reagent and a reduced incidence of the disease, compared to untreated animals bearing the transgene would indicate a potential therapeutic intervention for the disease. Alternatively, the non-human homologues of B7-2 can be used to construct a B7-2 "knock out" animal which has a defective B7-2 gene. Such animals can be characterized for their ability to accept grafts, reject tumors and defend against infectious diseases.

Detailed Description Paragraph Right (48):
More specifically, given the structure and function of the novel B lymphocyte activation antigens disclosed herein, it is possible to upregulate or down regulate the function of a B lymphocyte antigen in a number of ways. Downregulating or preventing one or more B lymphocyte antigen functions, i.e., preventing high level lymphokine synthesis by activated T cells, should be useful in treating autoimmune diseases such as rheumatoid arthritis and multiple sclerosis and also in tissue and organ transplantation and graft versus host disease. For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation.

Typically, in tissue transplants, rejection of the transplant is initiated by its recognition as foreign, followed by an immune reaction that destroys the transplant. The administration of a soluble, monomeric form of B7-2 alone or in conjuntion with a monomeric form of another B lymphocyte antigen (e.g., B7-1, B7-3) or blocking antibody, prior to transplantation can lead to the binding of the monomeric antigen(s) to its natural ligand(s) on T cells without transmitting the corresponding costimulatory signal and thus blocks the ligand(s) on T cells. Blocking B lymphocyte antigen function in this manner prevents T cell lymphokine synthesis and thus acts as an immunosuppressant. Moreover, the lack of costimulation may also be sufficient to induce T cell tolerance in a subject. It may also be necessary to block the function of a combination of B lymphocyte antigens to acheive sufficient immunosuppression or tolerance in a subject. For example, it may be desirable to block the function of both B7-2 and B7-1, B7-2 and B7-3, B7-1 and B7-3 or B7-2, B7-1 and B7-3 by administering a soluble form of each of these antigens prior to transplantation or in the treatment of an autoimmune disease.

Detailed Description Paragraph Right (66):
The term antibody as used herein is intended to include fragments thereof which are also specifically reactive with the novel B lymphocyte antigens described herein or portion thereof. Antibodies can be fragmented using conventional techniques and the fragments screened for utility in the same manner as described above for whole antibodies. For example, F(ab').sub.2 fragments can be generated by treating antibody with pepsin. The resulting F(ab').sub.2 fragment can be treated to reduce disulfide bridges to produce Fab' fragments. The antibody of the present invention is further intended to include bispecific and chimeric molecules having an anti-B lymphocyte activation antigen (i.e., B7-2, B7-3) portion.

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Search Results - Record(s) 11 through 14 of 14 returned.

☐ 11. Document ID: US 5942607 A

L5: Entry 11 of 14 File: USPT Aug 24, 1999

US-PAT-NO: 5942607
DOCUMENT-IDENTIFIER: US 5942607 A

TITLE: B7-2: a CTLA4/CD28 ligand

DATE-ISSUED: August 24, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Freeman; Gordon J.	Brookline	MA		
Nadler; Lee M.	Newton	MA		
Gray; Gary S.	Brookline	MA		

US-CL-CURRENT: 536/23.5; 530/350

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments   KWIC | Draw Desc | Image

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☐ 12. Document ID: US 5916910 A

L5: Entry 12 of 14 File: USPT Jun 29, 1999

US-PAT-NO: 5916910
DOCUMENT-IDENTIFIER: US 5916910 A

TITLE: Conjugates of dithiocarbamates with pharmacologically active agents and uses therefore

DATE-ISSUED: June 29, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Lai; Ching-San	Encinitas	CA		

US-CL-CURRENT: 514/423; 514/514, 548/564, 548/573, 558/235

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments   KWIC | Draw Desc | Image

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☐ 13. Document ID: US 5837544 A

L5: Entry 13 of 14 File: USPT Nov 17, 1998

US-PAT-NO: 5837544
DOCUMENT-IDENTIFIER: US 5837544 A

TITLE: Method of inducing a cell to proliferate using a chimeric receptor comprising janus kinase

DATE-ISSUED: November 17, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Capon; Daniel J.	Hillsborough	CA		
Tian; Huan	Cupertino	CA		
Smith; Douglas H.	Foster City	CA		
Winslow; Genine A.	Hayward	CA		
Siekevitz; Miriam	New York	NY		

US-CL-CURRENT: 435/375; 435/325, 435/376, 435/377, 435/69.7

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments   KWIC | Draw Desc | Image

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☐ 14. Document ID: US 5741899 A

L5: Entry 14 of 14   File: USPT   Apr 21, 1998

US-PAT-NO: 5741899
DOCUMENT-IDENTIFIER: US 5741899 A

TITLE: Chimeric receptors comprising janus kinase for regulating cellular pro liferation

DATE-ISSUED: April 21, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Capon; Daniel J.	Hillsborough	CA		
Tian; Huan	Cupertino	CA		
Smith; Douglas H.	Foster City	CA		
Winslow; Genine A.	Hayward	CA		
Siekevitz; Miriam	New York	NY		

US-CL-CURRENT: 536/23.4; 435/320.1, 435/325, 435/377, 435/69.7, 530/350, 530/387.3

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments   KWIC | Draw Desc | Image

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☑ 11. Document ID: US 5942607 A

L5: Entry 11 of 14 File: USPT Aug 24, 1999

US-PAT-NO: 5942607
DOCUMENT-IDENTIFIER: US 5942607 A

TITLE: B7-2: a CTLA4/CD28 ligand

DATE-ISSUED: August 24, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Freeman; Gordon J.	Brookline	MA		
Nadler; Lee M.	Newton	MA		
Gray; Gary S.	Brookline	MA		

US-CL-CURRENT: 536/23.5; 530/350

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

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☐ 12. Document ID: US 5916910 A

L5: Entry 12 of 14 File: USPT Jun 29, 1999

US-PAT-NO: 5916910
DOCUMENT-IDENTIFIER: US 5916910 A

TITLE: Conjugates of dithiocarbamates with pharmacologically active agents and uses therefore

DATE-ISSUED: June 29, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Lai; Ching-San	Encinitas	CA		

US-CL-CURRENT: 514/423; 514/514, 548/564, 548/573, 558/235

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

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☐ 13. Document ID: US 5837544 A

L5: Entry 13 of 14 File: USPT Nov 17, 1998

US-PAT-NO: 5837544
DOCUMENT-IDENTIFIER: US 5837544 A

TITLE: Method of inducing a cell to proliferate using a chimeric receptor comprising janus kinase

DATE-ISSUED: November 17, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Capon; Daniel J.	Hillsborough	CA		
Tian; Huan	Cupertino	CA		
Smith; Douglas H.	Foster City	CA		
Winslow; Genine A.	Hayward	CA		
Siekevitz; Miriam	New York	NY		

US-CL-CURRENT: 435/375; 435/325, 435/376, 435/377, 435/69.7

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments   KWIC | Draw Desc | Image

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☐ 14. Document ID: US 5741899 A

L5: Entry 14 of 14   File: USPT   Apr 21, 1998

US-PAT-NO: 5741899
DOCUMENT-IDENTIFIER: US 5741899 A

TITLE: Chimeric receptors comprising janus kinase for regulating cellular pro liferation

DATE-ISSUED: April 21, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Capon; Daniel J.	Hillsborough	CA		
Tian; Huan	Cupertino	CA		
Smith; Douglas H.	Foster City	CA		
Winslow; Genine A.	Hayward	CA		
Siekevitz; Miriam	New York	NY		

US-CL-CURRENT: 536/23.4; 435/320.1, 435/325, 435/377, 435/69.7, 530/350, 530/387.3

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments   KWIC | Draw Desc | Image

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L5: Entry 1 of 14 File: PGPB Dec 27, 2001

PGPUB-DOCUMENT-NUMBER: 20010056066
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20010056066 A1

TITLE: Method of treating immune cell mediated systemic diseases

PUBLICATION-DATE: December 27, 2001

US-CL-CURRENT: 514/8; 424/131.1

APPL-NO: 09/ 905836 [PALM]
DATE FILED: July 13, 2001

RELATED-US-APPL-DATA:

RLAN	RLFD	RLPC	RLKC	RLAC
09905836	Jul 13, 2001	ABANDONED	A1	US
09230119	May 26, 1999	UNKNOWN		US
09230119	May 26, 1999			WO
PCT/US97/12600	Jul 25, 1997			US
60022472	Jul 26, 1996			

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L9: Entry 31 of 53 File: USPT Oct 10, 2000

DOCUMENT-IDENTIFIER: US 6130316 A
TITLE: Fusion proteins of novel CTLA4/CD28 ligands and uses therefore

Brief Summary Paragraph Right (15):
Another embodiment of the invention provides antibodies, preferably monoclonal antibodies, specifically reactive with a peptide of a novel B lymphocyte antigen or fusion protein as described herein. Preferred antibodies are anti-human B7-2 monoclonal antibodies produced by hybridoma cells HF2.3D1, HA5.2B7 and HA3.1F9. These hybridoma cells have been deposited with the American Type Culture Collection at ATCC Accession No. HB 11686 (HF2.3D1), ATCC Accession No. HB 11687 (HA5.2B7), and ATCC Accession No. HB 11688.

Brief Summary Paragraph Right (18):
The invention also provides methods for inducing both general immunosuppression and antigen-specific tolerance in a subject by, for example, blocking the functional interaction of the novel B lymphocyte antigens of the invention, e.g., B7-2 and B7-3, to their natural ligand(s) on T cells or other immune system cells, to thereby block co-stimulation through the receptor-ligand pair. In one embodiment, inhibitory molecules that can be used to block the interaction of the natural human B7-2 antigen to its natural ligands (e.g., CTLA4 and CD28) include a soluble peptide having B7-2 binding activity but lacking the ability to costimulate immune cells, antibodies that block the binding of B7-2 to its ligands and fail to deliver a co-stimulatory signal (so called "blocking antibodies", such as blocking anti-B7-2 antibodies), B7-2-Ig fusion proteins, which can be produced in accordance with the teachings of the present invention, as well as soluble forms of B7-2 receptors, such as CTLA4Ig or CD28Ig. Such blocking agents can be used alone or in combination with agents which block interaction of other costimulatory molecules with their natural ligands (e.g., anti-B7 antibody). Inhibition of T cell responses and induction of T cell tolerance according to the methods described herein may be useful prophylactically, in preventing transplantation rejection (solid organ, skin and bone marrow) and graft versus host disease, especially in allogeneic bone marrow transplantation. The methods of the invention may also be useful therapeutically, in the treatment of autoimmune diseases, allergy and allergic reactions, transplantation rejection, and established graft versus host disease in a subject.

Drawing Description Paragraph Right (12):
FIG. 12 is a graphic representation of the inhibition by mAbs and recombinant proteins of the proliferation of CD28+ T cells, as assessed by .sup.3 H-thymidine incorporation and IL-2 secretion, to stimulation by PMA and COS cells transfected with vector alone (vector), or with a vector expressing B7-1 (B7-1) or B7-2 (B7-2). Inhibition studies were performed with the addition of either no antibody (no mAb), anti-B7 mab 133 (133), anti-B7 mAb BB-1 (BB1), anti-B5 mAb (B5), Fab fragment of anti-CD28 (CD28 Fab), CTLA4Ig (CTLA4Ig), or Ig control protein (control Ig) to the PMA stimulated COS cell admixed CD28.sup.+ T cells.

Drawing Description Paragraph Right (17):
FIG. 17 depicts flow cytometric profiles of cells stained with an anti-hB7-2 monoclonal antibody, HA3.1F9. Cells stained with the antibody were CHO cells transfected to express human B7-2 (CHO-hB7.2), NIH 3T3 cells transfected to express human B7-2 (3T3-hB7.2) and control transfected NIH 3T3 cells (3T3-neo). The anti-hB7.2 antibody B70 was used as a positive control.

Drawing Description Paragraph Right (18):

FIG. 18 depicts flow cytometric profiles of cells stained with an anti-hB7-2 monoclonal antibody, HA5.2B7. Cells stained with the antibody were CHO cells transfected to express human B7-2 (CHO-hB7.2), NIH 3T3 cells transfected to express human B7-2 (3T3-hB7.2) and control transfected NIH 3T3 cells (3T3-neo). The anti-hB7.2 antibody B70 was used as a positive control.

Drawing Description Paragraph Right (19):
FIG. 19 depicts flow cytometric profiles of cells stained with an anti-hB7-2 monoclonal antibody, HF2.3D1. Cells stained with the antibody were CHO cells transfected to express human B7-2 (CHO-hB7.2), NIH 3T3 cells transfected to express human B7-2 (3T3-hB7.2) and control transfected NIH 3T3 cells (3T3-neo). The anti-hB7.2 antibody B70 was used as a positive control.

Detailed Description Paragraph Right (2):
The B lymphocyte antigen B7-2 is expressed by human B cells at about 24 hours following stimulation with either anti-immunoglobulin or anti-MHC class II monoclonal antibody. The B7-2 antigen induces detectable IL-2 secretion and T cell proliferation. At about 48 to 72 hours post activation, human B cells express both B7-1 and a third CTLA4 counter-receptor, B7-3, identified by a monoclonal antibody BB-1, which also binds B7-1 (Yokochi, T., et al. (1982) J. Immunol. 128, 823-827). The B7-3 antigen is also expressed on B7-1 negative activated B cells and can costimulate T cell proliferation without detectable IL-2 production, indicating that the B7-1 and B7-3 molecules are distinct. B7-3 is expressed on a wide variety of cells including activated B cells, activated monocytes, dendritic cells, Langerhan cells and keratinocytes. At 72 hours post B cell activation, the expression of B7-1 and B7-3 begins to decline. The presence of these costimulatory molecules on the surface of activated B lymphocytes indicates that T cell costimulation is regulated, in part, by the temporal expression of these molecules following B cell activation.

Detailed Description Paragraph Right (24):
Suitable cells for use in isolating nucleic acids encoding peptides having an activity of a novel B lymphocyte antigen include cells capable of producing mRNA coding for B lymphocyte antigens (e.g., B7-1, B7-2, B7-3) and appropriately translating the mRNA into the corresponding protein. One source of mRNA is normal human splenic B cells, either resting or activated by treatment with an anti-immunoglobulin antibody or an anti-MHC class II antibody, or from subsets of neoplastic B cells. Expression of the human B7-2 antigen is detectable in resting B cells and in activated B cells, with mRNA levels increasing 4-fold from resting levels following stimulation. Total cellular RNA can be obtained using standard techniques from resting or activated B cells during these intervals and utilized in the construction of a cDNA library.

Detailed Description Paragraph Right (26):
B7-3 and can alternatively serve as a source of the mRNA for construction of a cDNA library. For example, tumor cells isolated from patients with non-Hodgkins lymphoma express B7-1 mRNA. B cells from nodular, poorly differentiated lymphoma (NPDL), diffuse large cell lymphoma (LCL) and Burkitt's lymphoma cell lines are also suitable sources of human B7-1 mRNA and, potentially B7-2 and B7-3 mRNA. Myelomas generally express B7-2, but not B7-1 mRNA, and, thus can provide a source of B7-2 mRNA. The Burkitt's lymphoma cell line Raji is one source of B lymphocyte antigen mRNA. Preferably, B7-2 mRNA is obtained from a population of both resting and activated normal human B cells. Activated B cells can be obtained by stimulation over a broad spectrum of time (e.g., from minutes to days) with, for example, an anti-immunoglobulin antibody or an anti-MCH class II antibody.

Detailed Description Paragraph Right (32):
According to one embodiment, plasmid DNA is introduced into a simian COS cell line (Gluzman, Cell 23:175 (1981)) by known methods of transfection (e.g., DEAE-Dextran) and allowed to replicate and express the cDNA inserts. The transfectants expressing B7-1 antigen are depleted with an anti-B7-1 monoclonal antibody (e.g., 133 and B1.1) and anti-murine IgG and IgM coated immunomagnetic beads. Transfectants expressing human B7-2 antigen can be positively selected by reacting the transfectants with the fusion proteins CTLA4Ig and CD28Ig, followed by panning with anti-human Ig antibody coated plates. Although human CTLA4Ig and CD28Ig fusion proteins were used in the examples described herein, given the cross-species reactivity between B7-1 and, for

example murine B7-1, it can be expected that other fusion proteins reactive with another cross-reactive species could be used. After panning, episomal DNA is recovered from the panned cells and transformed into a competent bacterial host, preferably E. coli. Plasmid DNA is subsequently reintroduced into COS cells and the cycle of expression and panning repeated at least two times. After the final cycle, plasmid DNA is prepared from individual colonies, transfected into COS cells and analyzed for expression of novel B lymphocyte antigens by indirect immunofluorescence with, for example, CTLA4Ig and CD28Ig.

Detailed Description Paragraph Right (38):
Alternatively, the non-human homologues of B7-2 can be used to construct a B7-2 "knock out" animal which has a defective or altered B7-2 gene as a result of homologous recombination between the endogenous B7-2 gene and altered B7-2 genomic DNA introduced into an embryonic cell of the animal. For example, murine B7-2 cDNA can be used to clone genomic B7-2 in accordance with established techniques. A portion of the genomic B7-2 DNA (e.g., such as an exon which encodes an extracellular domain) can be deleted or replaced with another gene, such as a gene encoding a selectable marker which can be used to monitor integration. Typically, several kilobases of unaltered flanking DNA (both at the 5' and 3' ends) are included in the vector (see e.g., Thomas, K. R. and Capecchi, M. R. (1987) Cell 51:503 for a description of homologous recombination vectors). The vector is introduced into an embryonic stem cell line (e.g., by electroporation) and cells in which the introduced DNA has homologously recombined with the endogenous DNA are selected (see e.g., Li, E. et al. (1992) Cell 69:915). The selected cells are then injected into a blastocyst of an animal (e.g., a mouse) to form aggregation chimeras (see e.g., Bradley, A. in Teratocarcinomas and Embryonic Stem Cells: A Practical Approach, E. J. Robertson, ed. (IRL, Oxford, 1987) pp. 113-152). A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term to create a "knock out" animal. Progeny harbouring the homologously recombined DNA in their germ cells can be identified by standard techniques and used to breed animals in which all cells of the animal contain the homologously recombined DNA. Knockout animals can be characterized for their ability to accept grafts, reject tumors and defend against infectious diseases and can be used in the study of basic immunobiology.

Detailed Description Paragraph Right (52):
Screening the peptides for those which retain a characteristic B lymphocyte antigen activity as described herein can be accomplished using one or more of several different assays. For example, the peptides can be screened for specific reactivity with an anti-B7-2 monoclonal antibody reactive with cell surface B7-2 or with a fusion protein, such as CTLA4Ig or CD28Ig. Specifically, appropriate cells, such as COS cells, can be transfected with a B7-2 DNA encoding a peptide and then analyzed for cell surface phenotype by indirect immunofluorescence and flow cytometry to determine whether the peptide has B7-2 activity. Cell surface expression of the transfected cells is evaluated using a monoclonal antibody specifically reactive with cell surface B7-2 or with a CTLA4Ig or CD28Ig fusion protein. Production of secreted forms of B7-2 is evaluated using anti-B7-2 monoclonal antibody or CTLA4Ig or CD28 fusion protein for immunoprecipitation.

Detailed Description Paragraph Right (54):
In vitro, T cells can be provided with a first or primary activation signal by anti-T3 monoclonal antibody (e.g. anti-CD3) or phorbol ester or, more preferably, by antigen in association with class II MHC. T cells which have received a primary activation signal are referred to herein as activated T cells. B7-2 function is assayed by adding a source of B7-2 (e.g., cells expressing a peptide having B7-2 activity or a secreted form of B7-2) and a primary activation signal such as antigen in association with Class II MHC to a T cell culture and assaying the culture supernatant for interleukin-2, gamrna interferon, or other known or unknown cytokine. For example, any one of several conventional assays for interleukin-2 can be employed, such as the assay described in Proc. Natl. Acad. Sci. USA, 86:1333 (1989) the pertinent portions of which are incorporated herein by reference. A kit for an assay for the production of interferon is also available from Genzyme Corporation (Cambridge, Mass.). T cell proliferation can also be measured as described in the Examples below. Peptides that retain the characteristics of the B7-2 antigen as described herein may result in increased per cell production of

cytokines, such as IL-2, by T cells and may also result in enhanced T cell proliferation when compared to a negative control in which a costimulatory signal is lacking.

Detailed Description Paragraph Right (64):
The peptides and fusion proteins produced from the nucleic acid molecules of the present invention can also be used to produce antibodies specifically reactive with B lymphocyte antigens. For example, by using a full-length B7-2 protein, or a peptide fragment thereof, having an amino acid sequence based on the predicted amino acid sequence of B7-2, anti-protein/anti-peptide polyclonal antisera or monoclonal antibodies can be made using standard methods. A mammal, (e.g., a mouse, hamster, or rabbit) can be immunized with an immunogenic form of the protein or peptide which elicits an antibody response in the mammal. The immunogen can be, for example, a recombinant B7-2 protein, or fragment thereof, a synthetic peptide fragment or a cell that expresses a B lymphocyte antigen on its surface. The cell can be for example, a splenic B cell or a cell transfected with a nucleic acid encoding a B lymphocyte antigen of the invention (e.g., a B7-2 cDNA) such that the B lymphocyte antigen is expressed on the cell surface. The immunogen can be modified to increase its immunogenicity. For example, techniques for conferring immunogenicity on a peptide include conjugation to carriers or other techniques well known in the art. For example, the peptide can be administered in the presence of adjuvant. The progress of immunization can be monitored by detection of antibody titers in plasma or serum. Standard ELISA or other immunoassay can be used with the immunogen as antigen to assess the levels of antibodies.

Detailed Description Paragraph Right (66):
The term antibody as used herein is intended to include fragments thereof which are also specifically reactive with a peptide having the activity of a novel B lymphocyte antigen or fusion protein as described herein. Antibodies can be fragmented using conventional techniques and the fragments screened for utility in the same manner as described above for whole antibodies. For example, F(ab').sub.2 fragments can be generated by treating antibody with pepsin. The resulting F(ab').sub.2 fragment can be treated to reduce disulfide bridges to produce Fab' fragments. The antibody of the present invention is further intended to include bispecific and chimeric molecules having an anti-B lymphocyte antigen (i.e., B7-2, B7-3) portion.

Detailed Description Paragraph Right (67):
Particularly preferred antibodies are anti-human B7-2 monoclonal antibodies produced by hybridomas HA3.1F9, HA5.2B7 and HF2.3D1. The preparation and characterization of these antibodies is described in detail in Example 8. Monoclonal antibody HA3.1F9 was determined to be of the IgG1 isotype; monoclonal antibody HA5.2B7 was determined to be of the IgG2b isotype; and monoclonal antibody HF2.3D1 was determined to be of the IgG2a isotype. Hybidoma cells were deposited with the American Type Culture Collection, which meets the requirements of the Budapest Treaty, on Jul. 19, 1994 as ATCC Accession No. HB 11688 (hybridoma HA3.1F9), ATCC Accession No. HB 11687 (HA5.2B7) and ATCC Accession No. HB 11686 (HF2.3D1).

Detailed Description Paragraph Right (68):
When antibodies produced in non-human subjects are used therapeutically in humans, they are recognized to varying degrees as foreign and an immune response may be generated in the patient. One approach for minimizing or eliminating this problem, which is preferable to general immunosuppression, is to produce chimeric antibody derivatives, i.e., antibody molecules that combine a non-human animal variable region and a human constant region. Chimeric antibody molecules can include, for example, the antigen binding domain from an antibody of a mouse, rat, or other species, with human constant regions. A variety of approaches for making chimeric antibodies have been described and can be used to make chimeric antibodies containing the immunoglobulin variable region which recognizes the gene product of the novel B lymphocyte antigens of the invention. See, for example, Morrison et al., Proc. Natl. Acad. Sci. U.S.A. 81:6851 (1985); Takeda et al., Nature 314:452 (1985), Cabilly et al., U.S. Pat. No. 4,816,567; Boss et al., U.S. Pat. No. 4,816,397; Tanaguchi et al., European Patent Publication EP171496; European Patent Publication 0173494, United Kingdom Patent GB 2177096B. It is expected that such chimeric antibodies would be less immunogenic in a human subject than the corresponding

non-chimeric antibody.

Detailed Description Paragraph Right (69):
For human therapeutic purposes, the monoclonal or chimeric antibodies specifically reactive with a peptide having the activity of a B lymphocyte antigen as described herein can be further humanized by producing human variable region chimeras, in which parts of the variable regions, especially the conserved framework regions of the antigen-binding domain, are of human origin and only the hypervariable regions are of non-human origin. General reviews of "humanized" chimeric antibodies are provided by Morrison, S. L. (1985) Science 229:1202-1207 and by Oi et al. (1986) BioTechniques 4:214. Such altered immunoglobulin molecules may be made by any of several techniques known in the art, (e.g., Teng et al., Proc. Natl. Acad Sci. U.S.A., 80:7308-7312 (1983); Kozbor et al., Immunology Today, 4:7279 (1983); Olsson et al., Meth. Enzymol., 92:3-16 (1982)), and are preferably made according to the teachings of PCT Publication WO92/06193 or EP 0239400. Humanized antibodies can be commercially produced by, for example, Scotgen Limited, 2 Holly Road, Twickenham, Middlesex, Great Britain. Suitable "humanized" antibodies can be alternatively produced by CDR or CEA substitution (see U.S. Pat. No. 5,225,539 to Winter; Jones et al. (1986) Nature 321:552-525; Verhoeyan et al. (1988) Science 239:1534; and Beidler et al. (1988) J. Immunol. 141:4053-4060). Humanized antibodies which have reduced immunogenicity are preferred for immunotherapy in human subjects. Immunotherapy with a humanized antibody will likely reduce the necessity for any concomitant immunosuppression and may result in increased long term effectiveness for the treatment of chronic disease situations or situations requiring repeated antibody treatments.

Detailed Description Paragraph Right (70):
As an alternative to humanizing a monoclonal antibody from a mouse or other species, a human monoclonal antibody directed against a human protein can be generated. Transgenic mice carrying human antibody repertoires have been created which can be immunized with a human B lymphocyte antigen, such as B7-2. Splenocytes from these immunized transgenic mice can then be used to create hybridomas that secrete human monoclonal antibodies specifically reactive with a human B lymphocyte antigen (see, e.g., Wood et al. PCT publication WO 91/00906, Kucherlapati et al. PCT publication WO 91/10741; Lonberg et al. PCT publication WO 92/03918; Kay et al. PCT publication 92/03917; Lonberg, N. et al. (1994) Nature 368:856-859; Green, L. L. et al. (1994) Nature Genet. 7:13-21; Morrison, S. L. et al. (1994) Proc. Natl. Acad. Sci USA 81:6851-6855; Bruggeman et al. (1993) Year Immunol 7:33-40; Tuaillon et al. (1993) PNAS 90:3720-3724; and Bruggeman et al. (1991) Eur J Immunol 21:1323-1326).

Detailed Description Paragraph Right (75):
The polyclonal or monoclonal antibodies of the current invention, such as an antibody specifically reactive with a recombinant or synthetic peptide having B7-2 activity or B7-3 activity can also be used to isolate the native B lymphocyte antigen from cells. For example, antibodies reactive with the peptide can be used to isolate the naturally-occurring or native form of B7-2 from activated B lymphocytes by immunoaffinity chromatography. In addition, the native form of B7-3 can be isolated from B cells by immunoaffinity chromatography with monoclonal antibody BB-1.

Detailed Description Paragraph Right (77):
The nucleic acid sequences and novel B lymphocyte antigens described herein can be used in the development of therapeutic reagents having the ability to either upregulate (e.g., amplify) or downregulate (e.g., suppress or tolerize) T cell mediated immune responses. For example, peptides having B7-2 activity, including soluble, monomeric forms of the B7-2 antigen or a B7-2 fusion protein, e.g., B7-2Ig, and anti-B7-2 antibodies that fail to deliver a costimulatory signal to T cells that have received a primary activation signal, can be used to block the B7-2 ligand(s) on T cells and thereby provide a specific means by which to cause immunosuppression and/or induce tolerance in a subject. Such blocking or inhibitory forms of B lymphocyte antigens and fusion proteins and blocking antibodies can be identified by their ability to inhibit T cell proliferation and/or cytokine production when added to an in vitro costimulation assay as previously described herein. In contrast to the monomeric form, stimulatory forms of B7-2, such as an intact cell surface B7-2, retain the ability to transmit the costimulatory signal to the T cells, resulting in

an increased secretion of cytokines when compared to activated T cells that have not received the secondary signal.

Detailed Description Paragraph Right (78):
In addition, fusion proteins comprising a first peptide having an activity of B7-2 fused to a second peptide having an activity of another B lymphocyte antigen (e.g., B7-1) can be used to modify T cell mediated immune responses. Alternatively, two separate peptides having an activity of B lymphocyte antigens, for example, B7-2 and B7-1, or a combination of blocking antibodies (e.g., anti-B7-2 and anti-B7-1 monoclonal antibodies) can be combined as a single composition or administered separately (simultaneously or sequentially), to upregulate or downregulate T cell mediated immune responses in a subject. recognition sequences may also be incorporated into the primers to allow for the cloning of the amplified fragment into a vector in a predetermined reading frame for expression.

Detailed Description Paragraph Right (82):
protein, or peptide fragment thereof, to identify and isolate packages that express an antibody having specificity for the B lymphocyte antigen. Nucleic acid encoding the selected antibody can be recovered from the display package (e.g., from the phage genome) and subcloned into other expression vectors by standard recombinant DNA techniques. Furthermore, a therapeutically active amount of one or more peptides having B7-2 activity and or B7-1 activity can be used in conjunction with other immunomodulating reagents to influence immune responses. Examples of other immunomodulating reagents include blocking antibodies, e.g., against CD28 or CTLA4, against other T cell markers or against cytokines, fusion proteins, e.g., CTLA4Ig, or immunosuppressive drugs, e.g., cyclosporine A or FK506.

Detailed Description Paragraph Right (87):
Downregulating or preventing one or more B lymphocyte antigen functions, e.g., preventing high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue transplants, rejection of the transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys the transplant. The administration of a molecule which inhibits or blocks interaction of a B7 lymphocyte antigen with its natural ligand(s) on immune cells (such as a soluble, monomeric form of a peptide having B7-2 activity alone or in conjunction with a monomeric form of a peptide having an activity of another B lymphocyte antigen (e.g., B7-1, B7-3) or blocking antibody), prior to transplantation can lead to the binding of the molecule to the natural ligand(s) on the immune cells without transmitting the corresponding costimulatory signal. Blocking B lymphocyte antigen function in this manner prevents cytokine synthesis by immune cells, such as T cells, and thus acts as an immunosuppressant. Moreover, the lack of costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigen-blocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens. For example, it may be desirable to block the function of B7-2 and B7-1, B7-2 and B7-3, B7-1 and B7-3 or B7-2, B7-1 and B7-3 by administering a soluble form of a combination of peptides having an activity of each of these antigens or a blocking antibody (separately or together in a single composition) prior to transplantation. Alternatively, inhibitory forms of B lymphocyte antigens can be used with other suppressive agents such as blocking antibodies against other T cell markers or against cytokines, other fusion proteins, e.g., CTLA4Ig, or immunosuppressive drugs.

Detailed Description Paragraph Right (88):
The efficacy of particular blocking reagents in preventing organ transplant rejection or GVHD can be assessed using animal models that are predictive of efficacy in humans. The functionally important aspects of B7-1 are conserved structurally between species and it is therefore likely that other B lymphocyte antigens can function across species, thereby allowing use of reagents composed of human proteins in animal systems. Examples of appropriate systems which can be used include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell

grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4Ig fusion proteins in vivo as described in Lenschow et al., Science, 257: 789-792 (1992) and Turka et al., Proc. Natl. Acad. Sci. USA, 89: 11102-11105 (1992). In addition, murine models of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of blocking B lymphocyte antigen function in vivo on the development of that disease.

Detailed Description Paragraph Right (90):
The IgE antibody response in atopic allergy is highly T cell dependent and, thus, inhibition of B lymphocyte antigen induced T cell activation may be useful therapeutically in the treatment of allergy and allergic reactions. An inhibitory form of B7-2 protein, such as a peptide having B7-2 activity alone or in combination with a peptide having the activity of another B lymphocyte antigen, such as B7-1, can be administered to an allergic subject to inhibit T cell mediated allergic responses in the subject. Inhibition of B lymphocyte antigen costimulation of T cells may be accompanied by exposure to allergen in conjunction with appropriate MHC molecules. Allergic reactions may be systemic or local in nature, depending on the route of entry of the allergen and the pattern of deposition of IgE on mast cells or basophils. Thus, it may be necessary to inhibit T cell mediated allergic responses locally or systemically by proper administration of an inhibitory form of B7-2 protein.

Detailed Description Paragraph Right (109):
The nucleic acid sequences encoding peptides having the activity of novel B lymphocyte antigens as described herein can be used to identify cytokines which are produced by T cells in response to stimulation by a form of B lymphocyte antigen, e.g., B7-2. T cells can be suboptimally stimulated in vitro with a primary activation signal, such as phorbol ester, anti-CD3 antibody or preferably antigen in association with an MHC class II molecule, and given a costimulatory signal by a stimulatory form of B7-2 antigen, for instance by a cell transfected with nucleic acid encoding a peptide having B7-2 activity and expressing the peptide on its surface or by a soluble, stimulatory form of the peptide. Known cytokines released into the media can be identified by ELISA or by the ability of an antibody which blocks the cytokine to inhibit T cell proliferation or proliferation of other cell types that is induced by the cytokine. An IL-4 ELISA kit is available from Genzyme (Cambridge Mass.), as is an IL-7 blocking antibody. Blocking antibodies against IL-9 and IL-12 are available from Genetics Institute (Cambridge, Mass.).

Detailed Description Paragraph Right (111):
To identify cytokines which prevent the induction of tolerance, an in vitro T cell costimulation assay as described above can be used. In this case, T cells would be given the primary activation signal and contacted with a selected cytokine, but would not be given the costimulatory signal. After washing and resting the T cells, the cells would be rechallenged with both a primary activation signal and a costimulatory signal. If the T cells do not respond (e.g., proliferate or produce IL-2) they have become tolerized and the cytokine has not prevented the induction of tolerance. However, if the T cells respond, induction of tolerance has been prevented by the cytokine. Those cytokines which are capable of preventing the induction of tolerance can be targeted for blockage in vivo in conjunction with reagents which block B lymphocyte antigens as a more efficient means to induce tolerance in transplant recipients or subjects with autoimmune diseases. For example, one could administer a B7-2 blocking reagent together with a cytokine blocking antibody to a subject.

Detailed Description Paragraph Right (115):
The monoclonal antibodies produced using the proteins and peptides of the current invention can be used in a screening assay for molecules which modulate the expression of B lymphocyte antigens on cells. For example, molecules which effect intracellular signaling which leads to induction of B lymphocyte antigens, e.g. B7-2 or B7-3, can be identified by assaying expression of one or more B lymphocyte antigens on the cell surface. Reduced immunofluorescent staining by an anti-B7-2 antibody in the presence of the molecule would indicate that the molecule inhibits intracellular signals. Molecules which upregulate B lymphocyte antigen expression result in an increased immunofluorescent staining. Alternatively, the effect of a molecule on expression of a B lymphocyte antigen, such as B7-2, can be determined by

detecting cellular B7-2 mRNA levels using a B7-2 cDNA as a probe. For example, a cell which expresses a peptide having B7-2 activity can be contacted with a molecule to be tested, and an increase or decrease in B7-2 mRNA levels in the cell detected by standard technique, such as Northern hybridization analysis or conventional dot blot of mRNA or total poly(A.sup.+)RNAs using a B7-2 CDNA probe labeled with a detectable marker. Molecules which modulate B lymphocyte antigen expression may be useful therapeutically for either upregulating or downregulating immune responses alone or in conjunction with soluble blocking or stimulating reagents. For instance, a molecule which inhibits expression of B7-2 could be administered together with a B7-2 blocking reagent for immunosuppressive purposes. Molecules which can be tested in the above-described assays include cytokines such as IL-4, .gamma.INF, IL-10, IL-12, GM-CSF and prostagladins.

Detailed Description Paragraph Right (136):
Phenotypic analysis of the B7-1+ and B7-1- activated splenic B cells confirmed the above functional results. FIG. 4 shows the cell surface expression of B7-1, B7-2 and B7-3 on fractionated B7-1.sup.+ and B7-1.sup.- activated B cell. As seen in FIG. 4, B7-1+ activated splenic B cells stained with anti-B7-1 (133) monoclonal antibody, BB-1 monoclonal antibody, and bound CTLA4-Ig. In contrast, B7- activated splenic B cells did not stain with anti-B7-1 (133) monoclonal antibody but did stain with BB-1 monoclonal antibody and CTLA4Ig. These phenotypic and functional results demonstrate that both B7-1+ and B7-1-activated (72 hours) human B lymphocytes express CTLA4 binding counter-receptor(s) which: 1) can induce submitogenically activated T cells to proliferate without detectable IL-2 secretion; and 2) are identified by the BB-1 monoclonal antibody but not anti-B7-1 monoclonal antibody. Thus, these CTLA4/CD28 ligands can be distinguished on the basis of their temporal expression after B cell activation and their reactivity with CTLA4Ig and anti-B7 monoclonal antibodies. The results of FIG. 4 are representative of five experiments.

Detailed Description Paragraph Right (138):
A series of experiments was conducted to determine whether the temporal expression of CTLA4 binding counter-receptors differentially correlated with their ability to costimulate T cell proliferation and/or IL-2 secretion. Human splenic CD28+ T cells submitogenically stimulated with anti-CD3 were cultured for 72 hours in the presence of irradiated human splenic B cells that had been previously activated in vitro by slg crosslinking for 24, 48, or 72 hours. IL-2 secretion was assessed by ELISA in supernatants after 24 hours and T cell proliferation as assessed by .sup.3 H-thymidine incorporation for the last 15 hours of a 72 hour culture. The results of FIG. 7 are representative of 5 experiments. As seen in FIG. 7a, 24 hour activated B cells provided a costimulatory signal which was accompanied by modest levels of IL-2 production, although the magnitude of proliferation was significantly less than observed with 48 and 72 hours activated human B cells (note differences in scale for .sup.3 H-Thymidine incorporation). Neither proliferation nor IL-2 accumulation was inhibited by anti-B7-1 (133) or BB-1. In contrast, with CTLA4Ig and anti-CD28 Fab monoclonal antibody totally abrogated proliferation and IL-2 accumulation. B cells activated for 48 hours, provided costimulation which resulted in nearly maximal proliferation and IL-2 secretion (FIG. 7b). Here, anti-B7-1 (133) monoclonal antibody, inhibited proliferation approximately 50% but totally blocked IL-2 accumulation. BB-1 monoclonal antibody totally inhibited both proliferation and IL-2 secretion. As above, CTLA4Ig and Fab anti-CD28 also totally blocked proliferation and IL-2 production. Finally, 72 hour activated B cells induced T cell response identical to that induced by 48 hour activated B cells. Similar results are observed if the submitogenic signal is delivered by phorbol myristic acid (PMA) and if the human splenic B cells are activated by MHC class II rather than Ig crosslinking. These results indicate that there are three CTLA4 binding molecules that are temporarily expressed on activated B cells and each can induce submitogenically stimulated T cells to proliferate. Two of these molecules, the early CTLA4 binding counter-receptor (B7-2) and B7-1 (133) induce IL-2 production whereas B7-3 induces proliferation without detectable IL-2 production.

Detailed Description Paragraph Right (143):
The B7-2 antigen is not detectable on activated B cells after 12 hours, but by 24 hours it is strongly expressed and functional. This molecule appears to signal via CD28 since proliferation and IL-2 production are completely blocked by Fab anti-CD28 monoclonal antibody. At 48 hours post activation, IL-2 secretion seems to be

accounted for by B7-1 costimulation, since anti-B7 monoclonal antibody completely inhibits IL-2 production.

Detailed Description Paragraph Right (145):
Two observations shed light on the biologic and potential clinical significance of these two additional CTLA4 binding counter-receptors. First, B7 (B7-1) deficient mouse has been developed and its antigen presenting cells were found to still bind CTLA4Ig (Freeman and Sharpe manuscript in preparation). This mouse is viable and isolated mononuclear cells induce detectable levels of IL-2 when cultured with T cells in vitro. Therefore, an alternative CD28 costimulatory counter-receptor or an alternative IL-2 producing pathway must be functional. Second, thus far the most effective reagents to induce antigen specific anergy in murine and human systems are CTLA4Ig and Fab anti-CD28, whereas anti-B7 monoclonal antibodies have been much less effective (Harding, F. A., et al. (1992) Nature. 356, 607-609; Lenschow, D. J., et al. (1992) Science. 257, 789-792; Chen, L., et al. (1992) Cell. 71, 1093-1102; Tan, P., et al. (1993) J. Exp. Med. 177, 165-173.). These observations are also consistent with the hypothesis that alternative CTLA4/CD28 ligands capable of inducing IL-2 exist, and taken together with the results presented herein, suggest that all three CTLA4 binding counter-receptors may be critical for the induction of T cell immunity. Furthermore, their blockade will likely be required for the induction of T cell anergy. Identical results have been observed in the murine system with the identification of two CTLA4 binding ligands, corresponding to the human B7-1 and B7-2 molecules. APCs in the B7 deficient mouse bind to the CTLA4 and can induce IL-2 secretion. Taken together, these observations indicate that multiple CTLA-4 binding counter-receptors exist and sequentially costimulate T cell activation in the murine system.

Detailed Description Paragraph Right (155):
In the first round of screening, thirty 100 mm dishes of 50% confluent COS cells were transfected with 0.05 .mu.g/ml anti-IgM activated human B cells library DNA using the DEAE-Dextran method (Seed et al., Proc. Natl. Acad. Sci. USA, 84:3365 (1987)). The cells were trypsinized and re-plated after 24 hours. After 47 hours, the cells were detached by incubation in PBS/0.5 mM EDTA, pH 7.4/0.02% Na azide at 37.degree. C. for 30 min. The detached cells were treated with 10 .mu.g/ml/CTLA4Ig and CD28Ig for 45 minutes at 4.degree. C.. Cells were washed and distributed into panning dishes coated with affinity-purified Goat anti-human IgG antibody and allowed to attach at room temperature. After 3 hours, the plates were gently washed twice with PBS/0.5 mM EDTA, pH 7.4/0.02% Na azide, 5% FCS and once with 0.15M NaCl, 0.01 M Hepes, pH 7.4, 5% FCS. Episomal DNA was recovered from the panned cells and transformed into E. coli DH10B/P3. The plasmid DNA was re-introduced into COS cells via spheroplast fusion as described (Seed et al., Proc. Natl. Acad. Sci. USA, 84:3365 (1987)) and the cycle of expression and panning was repeated twice. In the second and third rounds of selection, after 47 hours, the detached COS cells were first incubated with .alpha.-B7-1 mAbs (133 and B1.1, 10 .mu.g/ml), and COS cells expressing B7-1 were removed by .alpha.-mouse IgG and IgM coated magnetic beads. COS cells were then treated with 10 .mu.g/ml of human CTLA4Ig (hCTLA4Ig) and human CD28Ig (hCD28Ig) and human B7-2 expressing COS cells were selected by panning on dishes with goat anti-human IgG antibody plates. After the third round, plasmid DNA was prepared from individual colonies and transfected into COS cells by the DEAE-Dextran method. Expression of B7-2 on transfected COS cells was analyzed by indirect immunofluorescence with CTLA4Ig.

Detailed Description Paragraph Right (162):
A. B7-2 Binds CTLA4Ig and Not Anti-B7-1 and Anti-B7-3 Monoclonal Antibodies

Detailed Description Paragraph Right (172):
Human CD28.sup.+ T cells were isolated by immunomagnetic bead depletion using mAbs directed against B cells, natural killer cells, and macrophages as previously described (Gimmi, C. D., Freeman, G. J., Gribben, J. G., Gray, G., Nadler, L. M. (1993) Proc. Natl. Acad. Sci USA 90, 6586-6590). B7-1, B7-2, and vector transfected COS cells were harvested 72 hours after transfection, incubated with 25 .mu.g/ml of mitomycin-C for 1 hour, and then extensively washed. 10.sup.5 CD28.sup.+ T cells were incubated with 1 ng/ml of phorbol myristic acetate (PMA) and 2.times.10.sup.4 COS transfectants. Blocking agents (10 .mu.g/ml) are indicated on the left side of FIG. 12 and include: 1) no monoclonal antibody (no blocking agents), 2) mAb 133

(anti-B7-1 mAb), 3) mAb BB1 (anti-B7-1 and anti-B7-3 mAb), 4) mAb B5 (control IgM mAb), 5) anti-CD28 Fab (mAb 9.3), 6) CTLA-Ig, and 7) control Ig. Panel a of FIG. 12 shows proliferation measured by .sup.3 H-thymidine (1 .mu.Ci) incorporation for the last 12 hours of a 72 hour incubation. FIG. 12, panel b, shows IL-2 production as measured by ELISA (Biosource, CA) using supernatants harvested 24 hours after the initiation of culture.

Detailed Description Paragraph Right (186):
COS cells expressing B7-1 were removed by .alpha.-mouse IgG and IgM coated magnetic beads. COS cells were then treated with 10 .mu.g/ml of human CTLA4Ig and murine CD28Ig and murine B7-2 expressing COS cells were selected by panning on dishes coated with goat anti-human IgG antibody. After the third round, plasmid DNA was prepared from individual colonies and transfected into COS cells by the DEAE-Dextran method. Expression of B7-2 on transfected COS cells was analyzed by indirect immunofluorescence with CTLA4Ig.

Detailed Description Paragraph Right (227):
Supernatants from the hybridomas HA3.1F9, HA5.2B7 and HF2.3D1 were further characterized by competitive ELISA, in which the ability of the monoclonal antibodies to inhibit the binding of biotinylated hCTLA4Ig to immobilized hB7-2 immunoglobulin fusion proteins was examined. Biotinylation of hCTLA4Ig was performed using Pierce Immunopure NHS-LC Biotin (Cat. No. 21335). B7-2 immunoglobulin fusion proteins used were: hB7.2-Ig (full-length hB7-2), hB7.2-VIg (hB7-2 variable domain only) and hB7.2-CIg (B7-2 constant domain only). A hB7.1 -Ig fusion protein was used as a control. For the ELISA, 96 well plates were coated with the Ig fusion protein (50 .mu.l/well of a 20 .mu.g/ml solution) overnight at room temperature. The wells were washed three times with PBS, blocked with 10% fetal bovine serum (FBS), 0.1% bovine serum albumin (BSA) in PBS for 1 hour at room temperature, and washed again three times with PBS. To each well was added 50 .mu.l of Bio-hCTLA4-Ig (70 ng/ml) and 50 .mu.l of competitor monoclonal antibody supernatant. Control antibodies were an anti-B7.1 mAb (EW3.5D12) and the anti-hB7-2 mAb B70 (IgG2b.kappa., obtained from Pharmingen). The wells were washed again and streptavidin-conjugated horse radish peroxidase (from Pierce, Cat. No.

Detailed Description Paragraph Left (17):
Production and Characterization of Monoclonal Antibodies to Human B7-2

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DOCUMENT-IDENTIFIER: US 6090914 A
TITLE: CTLA4/CD28Ig hybrid fusion proteins and uses thereof

Abstract Paragraph Left (1):
The invention identifies the CTLA4 receptor as a ligand for the B7 antigen. The complete amino acid sequence encoding human CTLA4 receptor gene is provided. Methods are provided for expressing CTLA4 as an immunoglobulin fusion protein, for preparing hybrid CTLA4 fusion proteins including CTLA4/CD28 chimeric proteins, and for using the soluble fusion proteins, fragments and derivatives thereof, including monoclonal antibodies reactive with B7 and CTLA4, to regulate T cell interactions and immune responses mediated by such interactions.

Brief Summary Paragraph Right (22):
There is a need for molecules which can identify in vitro B7 positive B cells, i.e., activated B cells, for leukocyte typing and FAC sorting. Further, there is a need for molecules which may be used to prevent the rejection of organ transplants and inhibit the symptoms associated with lupus erythmatosus and other autoimmune diseases. In the past, major therapies relied on panimmunosuppressive drugs, such as cyclosporine A or monoclonal antibodies (MAbs) to CD3 to prevent organ transplants or inhibit symptoms of lupus. Unfortunately, these drugs must frequently be taken for the life of the individual, depress the entire immune system, and often produce secondary health ailments such as increased frequency of infections and cancer.

Brief Summary Paragraph Right (23):
Accordingly, the present invention provides the complete and correct DNA sequence encoding the amino acid sequence corresponding to the CTLA4 receptor protein, and identifies B7 antigen (e.g. B7-1 and B7-2 antigens) as a natural ligand for the CTLA4 receptor. The invention also provides a method for expressing the DNA as a CTLA4 immunoglobulin (Ig) fusion protein product. Embodiments of the invention include CTLA4Ig fusion protein, and hybrid fusion proteins including CD28/CTLA4Ig fusion proteins (which is also referred to herein as the CTLA4/CD28Ig fusion protein). Also provided are methods for using the CTLA4 fusion protein, B7Ig fusion protein, hybrid fusion proteins, and fragments and/or derivatives thereof, such as monoclonal antibodies reactive with CTLA4 and the B7 antigen, to regulate cellular interactions and immune responses.

Brief Summary Paragraph Right (35):
Also, the invention provides method for inhibiting tissue transplant rejection by a subject, the subject being a recipient of transplanted tissue. This method comprises administering to the subject a B7-binding molecule and an IL4-binding molecule.

Brief Summary Paragraph Right (36):
The present invention further provides a method for inhibiting graft versus host disease in a subject which comprises administering to the subject a B7-binding molecule and an IL4-binding molecule.

Drawing Description Paragraph Right (12):
FIGS. 12A, 12B, 12C, and 12D are photographs of histopathology slides of human islets transplanted under the kidney capsule of B10 mice.

Drawing Description Paragraph Right (13):
FIG. 13 is a line graph showing the prolongation of islet graft survival with MAb to human B7.

Drawing Description Paragraph Right (14):
FIG. 14 is a line graph showing induction of donor-specific unresponsiveness to islet graft antigens by CTLA4Ig.

Detailed Description Paragraph Right (24):
Also, the present invention provides a method for inhibiting tissue transplant rejection by a subject, the subject being a recipient of transplanted tissue. This method can comprise administering to the subject a B7-binding molecule and an IL4-binding molecule.

Detailed Description Paragraph Right (25):
The invention further provides a method for inhibiting graft versus host disease in a subject which comprises administering to the subject a B7-binding molecule and an IL4-binding molecule.

Detailed Description Paragraph Right (54):
The B7 antigen expressed on activated B cells and cells of other lineages, and the CD28 receptor expressed on T cells, can directly bind to each other, and this interaction can mediate cell-cell interaction. Such interactions directly trigger the CD28 activation pathway in T cells, leading to cytokine production, T cell proliferation, and B cell differentiation into immunoglobulin producing cells. The activation of B cells that occurs, can cause increased expression of B7 antigen and further CD28 stimulation, leading to a state of chronic inflammation such as in autoimmune diseases, allograft rejection, graft versus host disease or chronic allergic reactions. Blocking or inhibiting this reaction may be effective in preventing T cell cytokine production and thus preventing or reversing inflammatory reactions.

Detailed Description Paragraph Right (69):
In another embodiment, the CTLA4Ig fusion protein may be used to identify additional compounds capable of regulating the interaction between CTLA4 and the B7 antigen. Such compounds may include small naturally occurring molecules that can be used to react with B cells and/or T cells. For example, fermentation broths may be tested for the ability to inhibit CTLA4/B7 interactions. In addition, derivatives of the CTLA4Ig fusion protein as described above may be used to regulate T cell proliferation. For example, the fragments or derivatives may be used to block T cell proliferation in graft versus host (GVH) disease which accompanies allogeneic bone marrow transplantation.

Detailed Description Paragraph Right (71):
Regulation of CTLA4-positive T cell interactions with B7 positive cells, including B cells, by the methods of the invention may thus be used to treat pathological conditions such as autoimmunity, transplantation, infectious diseases and neoplasia.

Detailed Description Paragraph Right (77):
Advantages of the Invention: The subject invention overcomes the problems associated with current therapies directed to preventing the rejection of tissue or organ transplants. In contrast to present therapies, the present invention affects only immunological responses mediated by B7 interactions.

Detailed Description Paragraph Right (78):
For example, the present invention affects the transplant antigen-specific T cells, thus inducing donor-specific and antigen-specific tolerance. The binding of CD28 by its ligand, B7/BB1 (B7), during T cell receptor engagement is critical for proper T cell signaling in some systems (M. K. Jenkins, P. S. Taylor, S. D. Norton, K. B. Urdahl, J. Immunol. 147:2461 (1991); C. H. June, J. A. Ledbetter, P. S. Linsley, C. B. Thompson, Immunol. Today 11:211 (1990); H. Reiser, G. J. Freeman, Z. Razi-Wolf, C. D. Gimmi, B. Benacerraf, L. M. Nadler, Proc. Natl. Acad. Sci. U.S.A. 89:271 (1992); N. K. Damie, K. Klussman, P. S. Linsley, A. Aruffo, J.Immunol. 148:1985 (1992)).

Detailed Description Paragraph Right (110):
mAbs. Murine monoclonal antibodies (mAbs) 9.3 (anti-CD28) and G19-4 (anti-CD3), G3-7 (anti-CD7), BB-1 (anti-B7 antigen) and rat mAb 187.1 (anti-mouse K chain) have been

described previously (Ledbetter et al., Proc. Natl. Acad. Sci. 84:1384-1388 (1987); Ledbetter et al., Blood 75:1531 (1990); Yokochi et al., supra) and were purified from ascites before use. The hybridoma producing mAb OKT8 was obtained from the ATCC, Rockville, Md., and the mAb was also purified from ascites before use. mAb 4G9 (anti-CD19) was provided by Dr. E. Engleman, Stanford University, Palo Alto, Calif.). Purified human-mouse chimeric mAb L6 (having human C.gamma.1 Fc portion) was a gift of Dr. P. Fell and M. Gayle (Bristol-Myers Squibb Pharmaceutical Research Institute, Seattle, Wash.).

Detailed Description Paragraph Right (143):
Human pancreatic islets cells were purified after collagenase digestion as described (C. Ricordi et al. Transplantation 52:519 (1991); A. G. Tzakis et al. Lancet 336:402 (1990); C. Ricordi, P. E. Lacy, E. H. Finke, B. J. Olack, D. W. Scharp, Diabetes 37:413 (1988)).

Detailed Description Paragraph Right (144):
B6 or B10 mice, treated with streptozocin (175 mg per kilogram of body weight) 3 to 5 days before transplant and exhibiting nonfasting plasma glucose levels of greater than 280 mg/dl (with the majority over 300 mg/ml), were used as recipients.

Detailed Description Paragraph Right (145):
Each animal received approximately 800 fresh human islets of 150 .mu.m in diameter beneath the left renal capsule (D. Faustman and C. Coe, Science 252:1700 (1991); Y. J. Zeng et al. Transplantation 53:277 (1992)). Treatment was started immediately after transplantation.

Detailed Description Paragraph Right (146):
Control animals were treated with PBS (solid lines) or L6 (dotted lines) at 50 .mu.g every other day for 14 days immediately after transplantation (FIG. 11A). Islet transplants were considered rejected when glucose levels were greater than 250 mg/dl for three consecutive days. Animals treated with PBS (n=14) and L6 (n=8) had mean graft survivals of 5.6 and 6.4 days, respectively.

Detailed Description Paragraph Right (147):
Animals were treated with 10 .mu.g of CTLA4Ig for 14 consecutive days immediately after transplant (n=7) (FIG. 11B). Three out of seven animals maintained their grafts for >80 days. The remaining four animals had a mean graft survival of 12.75 days.

Detailed Description Paragraph Right (148):
Animals were treated with 50 .mu.g of CTLA4Ig every other day for 14 days immediately after human islet transplantation (FIG. 11C). All animals (n=12) treated with this dose maintained grafts throughout the analysis (FIG. 11C). Selected mice were nephrectomized on days 21 and 29 after the transplant to assess the graft's function (FIG. 11C).

Detailed Description Paragraph Right (149):
Histology was performed on kidneys transplanted with human islet cells (FIGS. 12A, 12B, 12C, 12D). The slides were analyzed blindly.

Detailed Description Paragraph Right (150):
Hematoxylin and eosin staining of a control human islet grafted mouse 29 days after transplantation showed a massive lymphocyte infiltration (FIG. 12A). The same tissue, stained for insulin, showed no detectable insulin production (FIG. 12B).

Detailed Description Paragraph Right (151):
Histological examination of tissue from a CTLA4Ig-treated mouse 21 days after transplant showed intact islets under the kidney capsule with very few lymphocytes infiltrating the transplanted tissue (FIG. 12C). The tissue was stained with hematoxylin and eosin. The same tissue from the CTLA4Ig-treated mouse, stained for insulin, showed the production of insulin by the grafted islets (FIG. 12D). Similar results were observed in graft tissue examined at later time points. The upper, middle, and lower arrowheads identify the kidney capsule, islet transplant, and kidney parenchyma, respectively.

Detailed Description Paragraph Right (153):
In FIG. 13 streptozotocin-treated animals were transplanted as described hereinabove for FIG. 11. The mice were treated either with PBS (dotted lines) or with MAb to human B7 (solid lines) at a dose of 50 .mu.g every other day for 14 days (FIG. 13). Control animals (treated with PBS) (n=3) had a mean graft survival of 3.5 days, whereas anti-B7-treated animals (n=5) maintained grafts from 9 to >50 days (FIG. 13).

Detailed Description Paragraph Right (154):
In FIG. 14 normal glycemic, CTLA4Ig-treated, transplanted mice (dotted lines) were nephrectomized on day 44 after transplant and immediately retransplanted with either 1000 first party donor islets (dotted lines, solid circles) or 1000 second party islets (dotted lines, open circles) beneath the remaining kidney capsule.

Detailed Description Paragraph Right (155):
These islets, frozen at the time of the first transplant, were thawed and cultured for 3 days before transplant to ensure islet function. B10 mice that had been treated with streptozotocin and exhibited nonfasting glucose levels of greater than 280 mg/dl were used as controls (solid lines) (FIG. 14). No treatment was given after transplantation.

Detailed Description Paragraph Right (156):
Control animals rejected both the first party (solid lines, closed circles) and the second party (solid lines, open circles) islet grafts by day 4 after transplant (FIG. 14). The CTLA4Ig-treated mice retransplanted with second party islets had a mean graft survival of 4.5 days, whereas animals retransplanted with first party donor islets maintained grafts for as long as analyzed (>80 days) (FIG. 14).

Detailed Description Paragraph Right (157):
C57BL/6 (B6) or C57BL/10 (B10) mice were treated with streptozotocin to eliminate mouse pancreatic islet B cell function. Diabetic animals were grafted under the kidney capsule, and treatment was started immediately after surgery. Survival of the islet grafts was monitored by the analysis of blood glucose concentrations.

Detailed Description Paragraph Right (158):
Transplanted control animals, treated with either phosphate-buffered saline (PBS)(n=14) or L6 (a human IgG1 chimeric MAb; n =8), had a mean graft survival of 5.6 and 6.4 days, respectively (FIG. 11A).

Detailed Description Paragraph Right (159):
In contrast, islet rejection was delayed in animals treated with CTLA4Ig (10 .mu.g per day for 14 days), with four out of the seven animals exhibiting moderately prolonged mean graft survival (12.75 days), whereas the remaining three animals maintained normal glucose levels for >80 days (FIG. 11B). This eventual increase in glucose concentration may be a result of islet exhaustion because no evidence of active cellular rejection was observed.

Detailed Description Paragraph Right (160):
In the three mice that maintained long-term islet grafts, the transient increase in glucose concentrations around day 21 after the transplant may have represented a self-limited rejection episode consistent with the pharmacokinetics of CTLA4Ig clearance after therapy (P. S. Linsley et al., Science 257:792 (1992)).

Detailed Description Paragraph Right (162):
In order to confirm that insulin production originated from the transplanted islets and not from the native mouse pancreas, we nephrectomized selected animals at days 21 and 29 to remove the islet grafts (FIG. 11C). In these animals, glucose concentrations increased to above 350 mg/dl within 24 hours, which indicated that the islet xenograft was responsible for maintaining normal glucose levels. It appears that the blocking of the CD28-B7 interaction inhibits xenogenic islet graft rejection.

Detailed Description Paragraph Right (163):
The effects of treatment with the soluble receptor, namely CTLAIg fusion protein, were not a result of Fc binding (L6 did not effect graft rejection) or general

effects on T cell or B cell function in vivo.

Detailed Description Paragraph Right (164):
Historical analyses of islet xenograft from control (PBS treated) and CTLA4Ig treated mice were done (FIGS. 12A, 12B, 12C, 12D). The islet tissue from the control animal demonstrated evidence of immune rejection, with a marked lymphocytic infiltrate into the graft and few remaining islets (FIG. 12A).

Detailed Description Paragraph Right (165):
Immunohistochemical staining showed that insulin-positive cells were present only rarely, and no somatostatin-positive cells were present at all (FIG. 12B). In contrast, transplant tissue from the CTLA4Ig-treated mice was devoid of any lymphocytic infiltrate (FIG. 12C).

Detailed Description Paragraph Right (166):
The grafts were intact, with many islets visible. In addition, the B cells observed in the human islet tissue produced human insulin (FIG. 12D) and somatostatin.

Detailed Description Paragraph Right (167):
The human CTLA4Ig used in this study reacts with both murine and human B7. One advantage of the xenogeneic transplant model is the availability of a MAb to human B7 that does not react with mouse B7 (T. Yokochi, R. D. Holly, E. A. Clark, J. Immunol. 128:823 (1982)). Thus, the role of human B7-bearing antigen-presenting cells (APCs) could be directly examined.

Detailed Description Paragraph Right (168):
The mice were transplanted as described and then treated with 50 .mu.g of MAb to human B7 every other day for 14 days after transplant. This treatment prolonged graft survival in treated mice (9 to >50 days) in comparison to that for control mice (FIG. 13). The anti-B7 MAb is unable to block rejection as effectively as CTLA4Ig.

Detailed Description Paragraph Right (169):
The CTLA4Ig therapy resulted in graft acceptance in the majority of mice. However, the animals may not be tolerant. Transient immunosuppression can lead to permanent islet graft acceptance because of graft adaptation (the loss of immunogenicity as a result of the loss of APC function) (L. Hao, Y. Wang, R. G. Gill, K. J. Lafferty, J. Immunol. 139:4022 (1987); K. J. Lafferty, S. J. Prowse, N. Simeonovic, Annu. Rev. Immunol. 1:143 (1983)).

Detailed Description Paragraph Right (171):
Streptozotocin-treated control animals, having never received an islet graft, were also transplanted with either first or second party islets. No treatment after the transplant was given. Control animals rejected the first and second party islets by day 4. The CTLA4Ig-treated animals that had received the second party islets rejected these islets by day 5, whereas animals receiving first party donor islets maintained the grafts for >80 days (FIG. 14).

Detailed Description Paragraph Left (5):
CTLA4Ig significantly prolongs human islet graft survival in mice in a donor-specific manner thereby providing an approach to immunosuppression

Other Reference Publication (2):
Lenschow et al. "Long-Term Survival of Xenogeneic Pancreatic Islet Grafts Induced by CTLA4Ig", Science 257:789-792 (1992). (Exhibit 69).

Other Reference Publication (46):
Storb, "Marrow Transplantation for Severe Aplastic Anemia: Methotrexate Alone Compared with a Combination of Methotrexate and Cyclosporine for Prevention of Acute Graft-Versus-Host Disease", Blood 56:119-125 (1986) (Exhibit 46).

Other Reference Publication (47):
Storb and Thomas, "Graft-Versus-Host Disease in Dog and Man: The Seattle Experience", Immunol. Rev. 88:215-238 (1985) (Exhibit 47).

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(('B7-2' OR CD86) SAME (ANTIBOD$) AND (ANTIBOD$) SAME (HUMANIZ$ OR HUMANIS$ OR CHIMERIC OR CHIMAERIC) AND (TRANSPLANT$ OR GRAFT$)).USPT,PGPB.	53

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L6	L3	0	L6
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L5	L3 and (transplant$ or graft$)	14	L5
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L3	('B7-2' or cd86) same (antibod$) same (humaniz$ or humanis$ or chimeric or chimaeric)	15	L3
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graft?)

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            5311  CD86
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         1302178  TRANSPLANT?
          471737  GRAFT?
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3/7/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13314961 BIOSIS NO.: 200100522110

Coadministration of either cyclosporine or steroids with humanized monoclonal **antibodies** against CD80 and **CD86** successfully prolong allograft survival after life supporting renal transplantation in cynomolgus monkeys.

AUTHOR: Hausen Bernard(a); Klupp Jochen; Christians Uwe; Higgins John P; Baumgartner Roxanne E; Hook Laurie E; Friedrich Stuart; Celnicker Abbie; Morris Randall E
AUTHOR ADDRESS: (a)Transplantation Immunology, Department of Cardiothoracic Surgery, Falk CVRB, Stanford University Medical Center, 300 Pasteur Drive, Palo Alto, CA, 94305-5407**USA

JOURNAL: Transplantation (Baltimore) 72 (6):p1128-1137 September 27, 2001
MEDIUM: print
ISSN: 0041-1337
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Background: Recent studies have shown some efficacy using monotherapy with monoclonal **antibodies** (mAb) against CD80 and **CD86** receptors after life-supporting renal transplantation in non-human primates. Our study was designed to evaluate the efficacy of combinations of the same mAbs with either microemulsion cyclosporine (CsA) or steroids. Methods: Unilateral renal transplantation was performed in 16 blood group-matched and MLR-mismatched cynomolgus monkeys that were assigned to four different treatment groups. All monkeys in groups I, II, and IV were treated with the combination of a CD80 (h1F1) and CD86 (h3D1) mAb given at 20 mg/kg each preoperatively, then 5 mg/kg at weekly intervals starting postoperative (po) day 0 until poday 56 (9 doses). In group I the animals (n=4) were treated with mAbs only. In group II (n=4) mAbs were combined with a CsA regimen adjusted daily to maintain target 24 hr trough levels of 150-300 ng/ml CsA for poday 0 to poday 56. In group III (n=4) the animals received CsA monotherapy according to the same regimen as group II. In group IV methylprednisone was administered at 2 mg/kg IV on poday 0-2, then at 0.5 mg/kg/day prednisone per gavage that was and tapered to 0.2 mg/kg/day on which they were maintained until poday 56. All animals were off all immunosuppressive treatment after poday 56 and were then followed until poday 119. Results: The mean survival of groups I-IV was 74 (range 9-119 days), 113 (96-119 days), 39 (22-71 days), and 79 days (6 to 119), respectively. All animals in group I showed clinical evidence of acute severe rejection (fever, creatinine increase, anuria) within the first week posttransplant, including those that retained renal function until poday 119. Only one animal in group II had a moderate clinical rejection during the treatment period and three of four animals survived the intended follow-up period. All animals in group III had multiple biopsy proven or severe clinical rejection episodes within the first 21 days and only one animal survived beyond poday 40. Moderate or severe acute rejection was diagnosed in three of four animals of group IV within the

first 28 days post **transplant** and only one animal survived until poday 119. Conclusion: Our data show that combining a calcineurin **inhibitor** or prednisone with mAbs designed to block costimulatory signals does not antagonize the immunosuppressive efficacy of these mAbs. In addition, combining CsA with mAbs directed against the CD80 and CD86 receptors significantly prolongs graft survival when compared to CsA monotherapy. Therefore clinical trials of humanized mAbs to CD80 and CD86 used in combination with conventional immunosuppression can be considered.

3/7/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12876013 BIOSIS NO.: 200100083162
Costimulatory blockade by the induction of an endogenous xenospecific antibody response.
AUTHOR: Rogers Nicola J; Mirenda Vincenzo; Jackson Ian; Dorling Anthony; Lechler Robert I(a)
AUTHOR ADDRESS: (a)Department of Immunology, Imperial College of Science, Technology and Medicine, Du Cane Road, Hammersmith Campus, London, W12 0NN: r.lechler@ic.ac.uk**UK
JOURNAL: Nature Immunology 1 (2):p163-168 August, 2000
MEDIUM: print
ISSN: 1529-2908
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RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Xenogeneic tissues induce vigorous T cell immunity, reflecting the ability of costimulatory molecules to function across species barriers. We describe a strategy to **inhibit** costimulation that exploits species differences using the model of porcine pancreatic islet **transplantation** into mice. Mice were immunized with chimeric peptides that contained a known T cell epitope and selected sequences of the porcine costimulatory molecule **CD86**. This resulted in anti-peptide **antibody** responses that recognized intact porcine **CD86**, blocked costimulation by porcine **CD86** but not murine **CD86** in vitro, and prolonged the survival of porcine islet grafts in vivo. This strategy of inducing endogenous donor-specific costimulatory blockade has potential clinical applicability.

3/7/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12582729 BIOSIS NO.: 200000336231
Anergic T cells generated in vitro suppress rejection response to islet allografts.
AUTHOR: Luo Zhi-Juan; Gotoh Mitsukazu(a); Grochowiecki Tadeusz; Tanaka Toshiyuki; Kimura Fumihiko; Kawashima Hiroto; Yagita Hideo; Okumura Ko; Miyasaka Masayuki
AUTHOR ADDRESS: (a)First Department of Surgery, Fukushima Medical University, 1 Hikarigaoka, Fukushima, 960-1295**Japan
JOURNAL: Transplantation (Baltimore) 69 (10):p2144-2148 May 27, 2000
MEDIUM: print
ISSN: 0041-1337
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Background. Induction of antigen-specific unresponsiveness to grafts is the ultimate goal for organ **transplantation**. It has been shown that anergic T cells generated in vivo can be transferred as **suppresser** cells. Anergic cells generated in vitro have never been successfully used to prevent allograft rejection in vivo. We examined whether anergic cells generated in vitro by blocking CD28/B7 costimulatory pathway can suppress allograft rejection in vivo. Methods. Anergic T cells were generated in vitro by the addition of anti-B7-1 and anti-**B7-2** monoclonal **antibodies** (mAbs) to primary mixed lymphocyte reaction (MLR) consisting of C57BL/6 (B6) splenocytes as responder and irradiated BALB/c splenocytes as stimulator. We tested the ability of these cells to respond to various stimuli and to **suppress** alloreactive T-cell responses in vitro. For in vivo studies, 4 X 107 anergic cells were injected intravenously immediately after **transplantation** of BALB/c islets under the renal sub-capsular space of streptozotocin-induced diabetic and 2.5-Gy X-irradiated B6 mice. Results. Anergic cells treated with both mAbs in the primary MLR did not proliferate in secondary MLR against BALB/c and third-party C3H/He stimulators. The cells also failed to respond to immobilized anti-CD3 mAb, although they proliferated in response to concanavalin A or phorbol myristate acetate + ionomycin. The anergic state was reversed by the addition of exogenous IL-2. Furthermore, these cells suppressed the proliferation of naive B6 T cells against either the same (BALB/c) or third-party (C3H/He) stimulator cells. In in vivo studies, irradiated B6 mice rejected BALB/c islet allografts acutely with a mean survival time of 27.0 +- 8.3 days, whereas two of six animals injected with the anergic cells accepted the allografts indefinitely (>100 days) with a mean survival time of 52.0 +- 38.2 days. Conclusions. Anergic cells generated in vitro by blocking CD28/B7 costimulatory pathway suppress islet allograft rejection after adoptive transfer. This procedure might be clinically useful for promoting allograft survival.

3/7/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12249827 BIOSIS NO.: 200000003329
Prevention of renal allograft rejection in primates by blocking the B7/CD28 pathway.
AUTHOR: Ossevoort Miriam A(a); Ringers Jan; Kuhn Eva-Maria; Boon Louis; Lorre Katrien; van den Hout Yvon; Bruijn Jan A; de Boer Mark; Jonker Margreet; de Waele Peter
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JOURNAL: Transplantation (Baltimore) 68 (7):p1010-1018 Oct. 15, 1999
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RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Background: There is accumulating evidence that blockade of the costimulatory pathways offers a valid approach for immune **suppression** after solid organ **transplantation**. In this study, the efficacy of anti-CD80 and anti-**CD86** monoclonal **antibodies** (mAbs) in combination with cyclosporine (CsA) to prevent renal allograft rejection was tested in non-human primates. Methods: Rhesus monkeys were transplanted with a partly major histocompatibility complex-matched kidney on day 0. Anti-CD80 and anti-CD86 mAbs were administered intravenously daily for 14 days starting at day -1. CsA was given intramuscularly for 35 days starting just after transplantation. The kidney function was monitored by determining serum creatinine levels.

Results: The combination of anti-CD80 and anti-CD86 mAbs completely abrogated the mixed lymphocyte reaction. Untreated rhesus monkeys rejected the kidney allograft in 5-7 days. Treatment with anti-CD80 plus anti-CD86 mAbs resulted in a significantly prolonged graft survi val of 28+-7 days (P=0.025). There were no clinical signs of side effects or rejection during treatment. Kidney graft rejection started after the antibody therapy was stopped. The anti-mouse antibody response was delayed from day 10 to 30 after the first injection. No difference in graft survival was observed between animals treated with CsA alone or in combination with anti-CD80 and anti-CD86 mAbs. However, treatment with anti-CD80 and anti-**CD86** mAbs reduced development of vascular rejection. Conclusions: In combination, anti-CD80 and anti-**CD86** mAbs abrogate T-cell proliferation in vitro, delay the anti-mouse **antibody** response in vivo, and prevent graft rejection and development of graft vascular disease in a preclinical vascularized transplant model in non-human primates.

3/7/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11490757 BIOSIS NO.: 199800272089
Increased expression of the novel molecule OX-2 is involved in prolongation of murine renal allograft survival.
AUTHOR: Gorczynski Reginald M(a); Chen Zhiqi; Fu Xin-Ming; Zeng Hua
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JOURNAL: Transplantation (Baltimore) 65 (8):p1106-1114 April 27, 1998
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DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Background. Portal venous (p.v.) peritransplant immunization with dendritic cells from bone marrow cultures, along with cyclosporine (10 mg/kg), produces antigen-specific increased renal allograft survival compared with recipients receiving intravenous (i.v.) immunization. Increased survival is associated with altered cytokine production from recipient T cells restimulated with donor antigen. We used a **suppressive** subtractive hybridization approach to explore a role in the regulation of **transplant** rejection for other genes differentially expressed after p.v. immunization. Methods. Subtractive hybridization was performed using tissue from p.v. and i.v. immunized mice and a novel polymerase chain reaction-based approach. A gene-bank search was used to identify the source of the differentially expressed cDNAs. One product, the mouse homologue of rat OX-2, was further analyzed using Western gels and FACS analysis of dendritic cells (NLDC145!+) isolated from p.v.-immunized mice. Results. Eighty cDNA clones were obtained by suppressive subtractive hybridization. Differential expression was confirmed in Northern RNA blots. One clone showed sequence homology to a gene encoding a molecule on rat dendritic cells (MRC OX-2), with homology to genes encoding the costimulatory molecules CD80 (B7-1) and **CD86** (**B7-2**). In p.v.-immunized mice, a monoclonal **antibody** to the rat OX-2 molecule identified, by Western blot analysis, increased expression of a molecule with molecular weight (43 kDa) analagous to rat MRC-OX-2; labels (by FACS analysis) indentified increased numbers of a population of cells staining with NLDC145; and blocks indentified increased graft survival. Conclusion. Our data suggest that OX-2 is functionally important in the increased graft survival seen in p.v.-immunized mice receiving renal allografts.

3/7/6 (Item 6 from file: 5)

11296736 BIOSIS NO.: 199800078068
Blockade of the CD40-CD40 ligand pathway potentiates the capacity of donor-derived dendritic cell progenitors to induce long-term cardiac allograft survival.
AUTHOR: Lu Lina(a); Li Wei; Fu Fumin; Chambers Frances G; Qian Shiguang; Fung John J; Thomson Angus W(a)
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JOURNAL: Transplantation (Baltimore) 64 (12):p1808-1815 Dec. 27, 1997
ISSN: 0041-1337
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RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Background: Failure of costimulatory molecule-deficient donor dendritic cells (DCs) to induce indefinite allograft acceptance may be a result of the "late" upregulation of these molecules on the DCs after interaction with host T cells. Ligation of CD40 on antigen-presenting cells by its cognate ligand CD40L is thought to induce expression of CD80 (B7-1) and **CD86** **(B7-2)**. We examined the influence of anti-CD40L monoclonal **antibody** (mAb) on the capacity of donor-derived DC progenitors to induce long-term allograft survival. Methods: High purity DC progenitors were grown from B10 (H2b) mouse bone marrow in granulocyte-macrophage colony-stimulating factor and transforming growth factor beta1 (TGFbeta1). Mature DC were propagated in granulocyte-macrophage colony-stimulating factor and interleukin-4. Their phenotype was characterized by flow cytometric analysis and their function by mixed leukocyte reactivity. Anti-donor cytotoxic T lymphocyte activity in grafts and spleens of vascularized heart allograft recipients was also assessed. Results: The TGFbeta-cultured cells were (1) DEC 205positive, MHC class II-positive, CD80dim, CD86dim, and CD40dim, (2) poor stimulators of naive allogeneic T-cell proliferation, and (3) able to prolong significantly BIO cardiac allograft survival in C3H (H2k) recipients when given (2 X 106 i.v.) 7 days before organ transplantation (median survival time (MST) 26 days vs. 12 day in controls, and 5 days in interleukin-4 DC-treated animals). Their allostimulatory activity was further diminished by addition of anti-CD40L mAb at the st of the mixed leukocyte cultures. Anti-CD40L alone (250 mug/mouse, i.p.; day -7) did not prolong cardiac graft survival (MST 12 days). In contrast, TGFbeta-cultured DCs + anti-CD40L mAb extended **graft** sur vival to a MST of 77 days, and **inhibited** substantiall the anti-donor cytotoxic T lymphocyte activity o **graft**-infiltrating cells and host spleen cells assessed days after **transplant**. Conclusions: The CD40-CD40L pathway appears important in regulation of allogeneic DC-T-cell functional interaction in vivo; its blockade increases markedly the potential of costimulatory molecule-deficient DCs of donor origin to induce long-lasting allograft survival.

3/7/7 (Item 7 from file: 5)

10974420 BIOSIS NO.: 199799595565
Analysis of the B7 costimulatory pathway in allograft rejection.
AUTHOR: Pearson Thomas C(a); Alexander Diane Z; Corbascio Matthias; Hendrix Rose; Ritchie Shannon C; Linsley Peter S; Faherty Denise; Larsen Christian P
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JOURNAL: Transplantation (Baltimore) 63 (10):p1463-1469 1997

ISSN: 0041-1337
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Background. Blockade of the B7/CD28 costimulation pathway with the fusion protein, CTLA4-Ig, has been shown to prolong allograft survival in numerous rodent models, suggesting that this pathway is functionally important in the allograft rejection response. This pathway is complex and consists of at least the B7-1, B7-1a, B7-1cyt II, and B7-2 molecules on the antigen-presenting cell and CD28 and CTLA4 molecules on the T cell. Methods. The intragraft transcript expression of the B7 molecules and their counterreceptors was defined using reverse transcriptase-polymerase chain reaction in the vascularized mouse cardiac allograft model. In addition, the functional significance of these molecules was investigated both in vitro in the mixed leukocyte response (MLR) and in vivo in the vascularized mouse cardiac allograft model. Results. Intragraft expression of B7-1, B7-1a, B7-1cyt II, B7-2, CD28, and CTLA4 transcripts is up-regulated in allografts when compared with both normal untransplanted hearts and syngeneic **transplants** at between 5 and 12 days after **transplant**. Both anti-B7-1 and anti-**B7-2** monoclonal **antibodies** alone **inhibited** T-cell proliferation in the MLR, however, equivalent maximal inhibition was obtained by a combination of these agents or by CTLA4-Ig. Likewise, in the mouse cardiac allograft model, both anti-B7-1 and anti-B7-2 modestly prolonged graft survival. However, an increased survival was obtained with either a combination of anti-B7-1 and anti-B7-2 or CTLA4-Ig. Blockade of the B7/CD28 pathway in the MLR using T cells from CD28 knockout mice had no effect on the proliferative response. Likewise, blockade of the B7/CD28 pathway did not effect the rate of rejection of cardiac allografts by CD28 knockout recipients. Conclusions. These data suggest that both B7-1 and B7-2 have an important role in allograft rejection in the mouse vascularized cardiac allograft model.

3/7/8 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10635894 BIOSIS NO.: 199699257039
Blockade of multiple costimulatory receptors induces hyporesponsiveness.
AUTHOR: Woodward Jennifer E; Qin Lihui; Chavin Kenneth D; Lin Jixun; Tono Takeshi; Ding Yaozhong; Linsley Peter S; Bromberg Jonathan S(a); Baliga Prabhakar
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JOURNAL: Transplantation (Baltimore) 62 (7):p1011-1018 1996
ISSN: 0041-1337
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LANGUAGE: English

ABSTRACT: T-lymphocyte activation requires engagement of the T cell receptor with antigen-major histocompatibility complex, and simultaneous ligation of costimulatory pathways via the lymphocyte receptors CD2 and CD28/CTLA4. Anti-CD2 monoclonal **antibody** (mAb) blocks the interaction of the antigen-presenting cell receptor CD48 with its ligand CD2, whereas CTLA4Ig binds with high affinity to the antigen-presenting cell ligands B7-1 and **B7-2**, blocking their interaction with CD28/CTLA4. We tested the immunosuppressive effects of simultaneously blocking both costimulatory pathways. Using donor C57BL/6J (H2-b) hearts transplanted to CBA/J (H2-k) recipients, anti-CD2 mAb plus CTLA4Ig administered at the time of transplantation prolonged cardiac allograft mean survival time to gt 120 days compared with untreated controls (12.2 +- 0.5 days, P lt 0.01), anti-CD2 mAb alone (24.8 +- 1.0 days, P lt

0.01), or CTLA4Ig alone (55.0 +- 2.0 days, P lt 0.01). Retransplantation of these recipients with donor-specific and third-party grafts demonstrated that hyporesponsiveness and tolerance were achieved. In vitro stimulation of lymphocytes from tolerant recipients with donor-specific alloantigen resulted in normal cytotoxic T lymphocyte and mixed lymphocyte reaction responses, showing that clonal deletion or anergy did not occur, but that **graft** adaptation or **suppression** likely helped to maintain long-term **graft** survival. In vitro combinations of anti-CD2 mAb and CTLA4Ig **suppressed** the generation of allogeneic cytotoxic T lymphocytes (58%) and the mixed lymphocyte reaction (36%); CTLA4Ig was more effective in this regard and the two agents were not synergistic. Anti-CD2 mAb and CTLA4Ig suppressed mitogen-driven proliferation in differential fashions, suggesting that they affected independent signaling pathways. Anti-CD2 mAb and CTLA4Ig also inhibited interleukin (IL)-2, IL-4, and IL-2 receptor (CD25). These data indicate that anti-CD2 mAb plus CTLA4Ig induces hyporesponsiveness and tolerance. The mechanism is likely related to the initial disruption of independent pathways of T-lymphocyte activation leading to antigen-specific long-term graft survival.

3/7/9 (Item 9 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10156792 BIOSIS NO.: 199698611710
Inhibition of **transplant** rejection following treatment with anti-**B7-2** and anti-B7-1 **antibodies**.
AUTHOR: Lenschow Deborah J; Zeng Yijun; Hathcock Karen S; Zuckerman Linda A ; Freeman Gordon; Thistlethwaite J Richard; Gray Gary S; Hodes Richard J; Bluestone Jeffrey A(a)
AUTHOR ADDRESS: (a)Committee Immunol., Ben May Inst., Dep. Pathol., MC1089, Univ. Chicago, Chicago, IL 60637**USA
JOURNAL: Transplantation (Baltimore) 60 (10):p1171-1178 1995
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DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Antigen-specific T cell activation depends initially on the interaction of the T cell receptor (TCR) with peptide/MHC. In addition, a costimulatory signal, mediated by distinct cell surface accessory molecules, is required for complete T cell activation leading to lymphokine production and proliferation. CD28 has been implicated as the major receptor on T cells responsible for delivering the costimulatory signal. Although two distinct ligands for CD28, B7-1 and B7-2, have been identified on antigen-presenting cells (APC), the costimulatory role of each molecule during a physiological immune response remains unresolved. In the present study, the relative roles of B7-1 and B7-2 interactions were evaluated in an allogeneic pancreatic islet **transplant** setting. In isolation, anti-B7-2 mAbs and, to a much lesser degree, anti-B7-1 mAbs **suppressed** T cell proliferative responses to allogeneic islets or splenic APC in vitro. Maximal inhibition of the allogeneic response was observed using a combination of the anti-B7-1 and anti-B7-2 mAbs. Administration of anti-B7-2 but not anti-B7-1 mAbs prolonged C3H allograft survival in B6 recipients, with a combination of both mAbs significantly prolonging rejection beyond either mAb alone. The immunosuppressive effects of the in vivo mAb treatment were not manifested in in vitro analyses as T cells isolated from suppressed mice responded normally to allogeneic stimuli in terms of both proliferation and lymphokine production. However, combined mAb therapy in vivo selectively delayed CD4+ T lymphocyte infiltration into the graft. These data suggest that both B7-1 and B7-2 costimulatory molecules are active in vivo, although B7-2 plays a clearly dominant role in this allograft

model. The mechanism of immune suppression in vivo remains unresolved but may occur at sites distinct from the allograft.

3/7/10 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

07850277 EMBASE No: 1999324063
The future of organ and tissue transplantation: Can T-cell costimulatory pathway modifiers revolutionize the prevention of graft rejection?
Harlan D.M.; Kirk A.D.
Dr. D.M. Harlan, Navy Medical Research Center, NIDDK, Navy Transplant./Autoimmunity Br., 8901 Wisconsin Ave, Bethesda, MD 20889 United States
Journal of the American Medical Association (J. AM. MED. ASSOC.) (United States) 15 SEP 1999, 282/11 (1076-1082)
CODEN: JAMAA ISSN: 0098-7484
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 68

Transplantation therapies have revolutionized care for patients with end-stage organ (kidney, liver, heart, lung, and pancreatic beta-cell) failure, yet significant problems persist with treatments designed to prevent graft rejection. Antirejection therapies are not always effective, must be taken daily, and are both expensive and associated with well-known toxic effects. Recent advances have suggested that the immune system has more self- regulatory capability than previously appreciated. In this review, we discuss immune system function and new therapeutic agents that modify so-called costimulatory receptor signaling to support **transplant** function without generally **suppressing** the immune system.

3/7/11 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE

07750268 EMBASE No: 1999232731
Human G-CSF-mobilized CD34-positive peripheral blood progenitor cells can stimulate allogeneic T-cell responses: Implications for graft rejection in mismatched transplantation
Van Rhee F.; Jiang Y.-Z.; Vigue F.; Kirby M.; Mavroudis D.; Hensel N.F.; Agarwala V.; Clave E.; Childs R.; Raptis A.; Sloand E.; Carter C.; Read E.J.; Barrett J.
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British Journal of Haematology (BR. J. HAEMATOL.) (United Kingdom) 1999, 105/4 (1014-1024)
CODEN: BJHEA ISSN: 0007-1048
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 26

To investigate mechanisms of stem cell graft rejection we studied the allo-stimulatory potential of G-CSF mobilized peripheral blood progenitor cells (PBPC). CD34sup + cells were purified (>95%) in a two-step procedure using immunoaffinity columns for CD34 selection and T-depletion. The capacity of CD34sup + cells to stimulate allogeneic T-cell responses was compared with other cells from the same individual. CD34sup + cells induced potent proliferative responses at stimulator:responder ratios of 1:20, but were approximately 50- fold less efficient compared to dendritic cells.

Furthermore, CD34sup + cells primed responses from partially matched allogeneic T cells in bulk cultures. Dual-colour flow cytometry showed that the co-stimulatory molecules B7.1, CD40 and ICAM-1 were absent on resting CD34-positive progenitor cells, but were induced during incubation with allogeneic lymphocytes due to a cytokine- mediated effect. Up-regulation of accessory molecules on CD34sup + cells was reproduced by incubation with interferon-gamma or GM-CSF which enhanced the allo-stimulatory activity of CD34sup + cells. Blocking studies with inhibitory **antibodies** suggested co-stimulatory functions for **B7**.**2**, ICAM-3, CD40 and LFA- 3. CD34sup + cells were more efficient in inducing allogeneic T-cell responses when compared to the unprocessed leukapheresis products. The reduced allo- stimulatory ability of G-CSF mobilized PBPC could be explained by the presence of CD3sup +4sup + and CD3sup +8sup + lymphocytes with **suppressor** activity. We conclude that current methods of stem cell selection for **transplantation** do not avoid allo-sensitization of the recipient and that further graft manipulation with add-back of lymphocytes or selection of subsets of CD34sup + cells with reduced allo-stimulatory ability may reduce graff rejection.

3/7/12 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE

07632387 EMBASE No: 1999115009
B7-2 expressed on EL4 lymphoma suppresses antitumor immunity by an interleukin 4-dependent mechanism
Stremmel C.; Greenfield E.A.; Howard E.; Freeman G.J.; Kuchroo V.K.
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Journal of Experimental Medicine (J. EXP. MED.) (United States) 15 MAR 1999, 189/6 (919-930)
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DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 38

For T cells to become functionally activated they require at least two signals. The B7 costimulatory molecules B7-1 and B7-2 provide the 'second signal' pivotal for T cell activation. In this report, we studied the relative roles of B7-1 and B7-2 molecules in the induction of antitumor immunity to the T cell thymoma, EL4. We generated EL4 tumor cells that expressed B7-1, B7-2, and B7-1+B7-2 by transfecting murine cDNAs. Our results demonstrate that EL4-B7-1 cells are completely rejected in syngeneic mice. Unlike EL4-B7-1 cells, we find that EL4-B7-2 cells are not rejected but progressively grow in the mice. A B7-1- and B7-2-EL4 double transfectant was generated by introducing B7-2 cDNA into the EL4-B7-1 tumor line that regressed in vivo. The EL4-B7-1+B7-2 double transfectant was not rejected when implanted into syngeneic mice but progressively grew to produce tumors. The double transfectant EL4 cells could costimulate T cell proliferation that could be blocked by anti-B7-1 **antibodies**, anti-**B7**-**2** **antibodies**, or hCTLA4 immunoglobulin, showing that the B7-1 and **B7**-**2** molecules expressed on the EL4 cells were functional. In vivo, treatment of mice implanted with double- transfected EL4 cells with anti-**B7**-**2** monoclonal **antibody** resulted in tumor rejection. Furthermore, the EL4-**B7**-**2** and EL4-B7-1+**B7**-**2** cells, but not the wild-type EL4 cells, were rejected in interleukin 4 (IL-4) knockout mice. Our data suggests that B7-2 expressed on some T cell tumors inhibits development of antitumor immunity, and IL-4 appears to play a critical role in abrogation of the antitumor immune response.

3/7/13 (Item 4 from file: 73)
DIALOG(R)File 73:EMBASE

07382731 EMBASE No: 1998295923
Rejection of the liver transplant
Knechtle S.J.
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Seminars in Gastrointestinal Disease (SEMIN. GASTROINTEST. DIS.) (United States) 1998, 9/3 (126-135)
CODEN: SGDIE ISSN: 1049-5118
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 65

Although the transplanted human liver is susceptible to rejection with a similar incidence of rejection as seen with renal allografts, the liver enjoys many immunological benefits relative to other transplanted organs. These include relative resistance to antibody-mediated injury, low frequency of chronic rejection, relatively easy reversibility of acute rejection, and even reversibility of chronic rejection. The reasons for the liver's favored status from an immunological perspective are unclear but are perhaps multifactorial. Currently used clinical protocols of immunosuppression for liver **transplantation** rely principally on the calcineurin **inhibitors**, cyclosporine and FK-506. Steroid withdrawal at variable periods after liver **transplantation** is becoming increasingly common. Compared with other organ **transplants**, relatively few human liver transplants are lost because of rejection. The transplanted liver may be an appropriate target for tolerance studies.

3/7/14 (Item 5 from file: 73)
DIALOG(R)File 73:EMBASE

06720020 EMBASE No: 1997001478
Costimulatory function and expression of CD40 ligand, CD80, and CD86 in vascularized murine cardiac allograft rejection
Hancock W.W.; Sayegh M.H.; Zheng X.-G.; Peach R.; Linsley P.S.; Turka L.A.
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Proceedings of the National Academy of Sciences of the United States of America (PROC. NATL. ACAD. SCI. U. S. A.) (United States) 1996, 93/24 (13967-13972)
CODEN: PNASA ISSN: 0027-8424
DOCUMENT TYPE: Journal; Conference Paper
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Recent data implicates a role for the CD40-CD40 ligand (CD40L) pathway in graft rejection. One potential mechanism is direct costimulation of T cells through CD40L. Alternatively, the ability of CD40 stimulation to induce CD80 (B7-1) and CD86 (B7-2) expression on antigen-presenting cells (APCs) has led to the hypothesis that the role of CD40-CD40L interactions in transplant rejection might be indirect, i.e., to promote the costimulatory capacity of APCs. Here, we have used a murine vascularized cardiac allograft model to test this hypothesis. Treatment of the recipients with donor splenocytes and a single dose of anti-CD40L mAb induces long-term **graft** survival (>100 days) in all animals. This is associated with marked **inhibition** of intragraft Th1 cytokine (interferon gamma and interleukin (IL) 2) and IL-12 expression with reciprocal up-regulation of

Th2 cytokines (IL-4 and IL-10). In untreated allograft recipients, CD86 is strongly expressed on endothelial cells and infiltrating mononuclear cells of the graft within 24 hr. In contrast, CD80 expression is nut seen until 72 hr after engraftment. Anti-CD40L mAb has no detectable effect on CD86 up-regulation, but almost completely abolishes induction of CD80. However, animals treated with anti- CD80 mAb or with a mutated form of CTLA4Ig (which does not bind to CD86) rejected their cardiac allografts, indicating that blockade of CD80 alone does not mediate the graft-prolonging effects of anti-CD40L mAb. These data support the notion that the role of CD40-CD40L in transplant rejection is not solely to promote CD80 or CD86 expression, but rather that this pathway can directly and independently costimulate T cells. These data also suggest that long-term graft survival can be achieved without blockade of either T cell receptor-mediated signals or CD28-CD86 engagement.

3/7/15 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10810582 99443397 PMID: 10515374

Increased apoptosis of immunoreactive host cells and augmented donor leukocyte chimerism, not sustained inhibition of B7 molecule expression are associated with prolonged cardiac allograft survival in mice preconditioned with immature donor dendritic cells plus anti-CD40L mAb.

Lu L; Li W; Zhong C; Qian S; Fung JJ; Thomson AW; Starzl TE

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Transplantation (UNITED STATES) Sep 27 1999, 68 (6) p747-57, ISSN 0041-1337 Journal Code: WEJ

Contract/Grant No.: AI41011, AI, NIAID; DK 29961, DK, NIDDK; DK49745, DK, NIDDK

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

BACKGROUND: We previously reported the association among donor leukocyte chimerism, apoptosis of presumedly IL-2-deficient graft-infiltrating host cells, and the spontaneous donor-specific tolerance induced by liver but not heart allografts in mice. Survival of the rejection-prone heart allografts in the same strain combination is modestly prolonged by the pretransplant infusion of immature, costimulatory molecule-(CM) deficient donor dendritic cells (DC), an effect that is markedly potentiated by concomitant CM blockade with anti-CD40L (CD154) monoclonal antibody (mAb). We investigated whether the long survival of the heart allografts in the pretreated mice was associated with donor leukocyte chimerism and apoptosis of graft-infiltrating cells, if these end points were similar to those in the spontaneously tolerant liver **transplant** model, and whether the pretreatment effect was dependent on sustained **inhibition** of CM expression of the infused immature donor DC. In addition, apoptosis was assessed in the host spleen and lymph nodes, a critical determination not reported in previous studies of either spontaneous or "treatment-aided" organ tolerance models. METHODS: Seven days before transplantation of hearts from B10 (H-2b) donors, 2x10(6) donor-derived immature DC were infused i.v. into C3H (H-2k) recipient mice with or without a concomitant i.p. injection of anti-CD40L mAb. Donor cells were detected posttransplantation by immunohistochemical staining for major histocompatibility complex class II (I-Ab) in the cells of recipient lymphoid tissue. CM expression was determined by two-color labeling. Host responses to donor alloantigen were quantified by mixed leukocyte reaction, and cytotoxic T lymphocyte (CTL) assays. Apoptotic death in graft-infiltrating cells and in areas of T-dependent lymphoid tissue was visualized by terminal deoxynucleotidyltransferase-catalyzed dUTP-digoxigen in nick-end labeling and quantitative spectrofluorometry. Interleukin-2 production and localization were estimated by immunohistochemistry. RESULTS: Compared with control heart transplantation or heart

transplantation after only DC administration, concomitant pretreatment with immature donor DC and anti-CD40L mAb caused sustained elevation of donor (I-Ab+) cells (microchimerism) in the spleen including T cell areas. More than 80% of the I-Ab+ cells in combined treatment animals also were CD86+, reflecting failure of the mAb to inhibit CD40/ CD80/CD86 up-regulation on immature DC in vitro after their interaction with host T cells. Donor-specific CTL activity in graft-infiltrating cells and spleen cell populations of these animals was present on day 8, but decreased strikingly to normal control levels by day 14. The decrease was associated with enhanced apoptosis of **graft**-infiltrating cells and of cells in the spleen where interleukin-2 production was **inhibited**. The highest levels of splenic microchimerism were found in mice with long surviving **grafts** (>100 days). In contrast, CTL activity was persistently elevated in control heart graft recipients with comparatively low levels of apoptotic activity and high levels of interleukin-2. CONCLUSION: The donor-specific acceptance of rejection-prone heart allografts by recipients pretreated with immature donor DC and anti-CD40L mAb is not dependent on sustained inhibition of donor DC CM (CD86) expression. Instead, the pretreatment facilitates a tolerogenic cascade similar to that in spontaneously tolerant liver recipients that involves: (1) chimerism-driven immune activation, succeeded by deletion of host immune responder cells by apoptosis in the spleen and allograft that is linked to interleukin-2 deficiency in both locations and (2) persistence of comparatively large numbers of donor-derived leukocytes. These tolerogenic mechanisms are thought to be generic, explaining the tolerance induced by allografts spontaneously, or with the aid of various kinds of immunosuppression.
Record Date Created: 19991105

3/7/16 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10801332 99138886 PMID: 9973463
The role of CD80, CD86, and CTLA4 in alloimmune responses and the induction of long-term allograft survival.
Judge TA; Wu Z; Zheng XG; Sharpe AH; Sayegh MH; Turka LA
Department of Medicine, University of Pennsylvania, Philadelphia 19104, USA.
Journal of immunology (UNITED STATES) Feb 15 1999, 162 (4) p1947-51, ISSN 0022-1767 Journal Code: IFB
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Document type: Journal Article
Record type: Completed
Blocking the interaction of the CD28 costimulatory receptor with its ligands, CD80 and CD86, inhibits in vivo immune responses, such as allograft rejection, and in some instances induces tolerance. Previously, we found that CTLA4Ig, which blocks the CD28/CTLA-4 (CD152) ligands CD80 and CD86, can be used to induce transplantation tolerance to vascularized allografts. Recent data suggest that an intact CD152-negative signaling pathway is essential for induction of tolerance to nominal Ags. Here, we show that blockade of CD152 using an anti-CD152 mAb at the time of transplantation prevents the induction of long-term allograft survival by agents that target CD80 and CD86. In contrast, CD152 signals are not required for the maintenance of established graft survival. We also report for the first time that blockade of CD86 alone can induce long-term graft survival. This requires that anti-CD86 mAb is given on the day of transplantation and also depends upon an intact CD152 pathway. This result, plus experiments using CD80-deficient mice, suggests a dominant role for CD80 molecules on donor cells as the relevant ligand for CD152. We additionally find that blockade of CD152 at the time of **transplantation** does not interfere with the effectiveness of anti-CD154 mAbs, suggesting distinct mechanisms for **inhibition** of

graft rejection by blocking the CD28 vs CD154 pathways.
Record Date Created: 19990413

3/7/17 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10746302 98149404 PMID: 9489760
Blockade of CD40-CD154 interferes with human T cell engraftment in scid mice.
Foy TM; McIlraith M; Masters SR; Dunn JJ; Rossini AA; Shultz LD; Hesselton RA; Wagar EJ; Lipsky PE; Noelle RJ; Greiner DL
Department of Microbiology, Dartmouth Medical School, Lebanon, NH 03756, USA.
Cell transplantation (UNITED STATES) Jan-Feb 1998, 7 (1) p25-35, ISSN 0963-6897 Journal Code: B02
Contract/Grant No.: A126926, PHS; AI30389, AI, NIAID; AI31229, AI, NIAID; +
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Antibodies to the ligand for CD40 (CD154) have been shown to exert profound effects on the development of cell-mediated immune responses in mice. The present study shows that an antibody to human CD154 (hCD40L) inhibits in vivo Tetanus toxoid (TT) specific secondary antibody responses in hu-PBL-scid mice, as well as the expansion of xenoreactive human T cells in the scid mice. A possible cause for the reduced expansion of xenoreactive, human T cells, was the decreased expression of murine B7.1 and B7.2 caused by the administration of anti-hCD40L. Therefore, it may be that defective maturation of murine antigen-presenting cells impeded the priming and expansion of human xenoreactive T cells.
Record Date Created: 19980413

3/7/18 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10212011 99343781 PMID: 10415071
An immunoadhesin incorporating the molecule OX-2 is a potent immunosuppressant that prolongs allo- and xenograft survival.
Gorczynski RM; Cattral MS; Chen Z; Hu J; Lei J; Min WP; Yu G; Ni J
Transplant Research Division, The Toronto Hospital, Canada. rgorczynski@transplantunit.org
Journal of immunology (UNITED STATES) Aug 1 1999, 163 (3) p1654-60, ISSN 0022-1767 Journal Code: IFB
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
We have established that, in mice receiving donor-specific immunization by the portal vein, the increased graft survival seen is associated with the increased expression of a molecule (OX-2) on a subpopulation of dendritic cells (DC), and polarization of cytokine production to type 2 cytokines on Ag-specific restimulation of cells from these mice. Furthermore, infusion of a mAb to OX-2 blocks both the increased graft survival and the altered cytokine production seen. We have constructed an immunoadhesin in which the extracellular domain of OX-2 is linked to the murine IgG2a Fc region, and we have expressed this molecule (OX-2:Fc) in a eukaryotic (baculovirus) expression system. Incubation of lymphocytes with 50 ng/ml OX-2:Fc inhibits a primary mixed lymphocyte reaction in vitro, as assayed by proliferation and induction of cytotoxic T cells, and also alters cytokine production with decreased IL-2 (IFN-gamma) production and increased IL-4 (IL-10) production. Similarly, in vivo infusion of OX-2:Fc promotes increased allo- and xenograft (both skin and renal grafts) survival and decreases the Ab response to sheep erythrocytes. Our data

suggest this molecule might have clinical importance in allo- and xenotransplantation.
Record Date Created: 19990812

3/7/19 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10012611 99113736 PMID: 9916698
Evidence that an OX-2-positive cell can inhibit the stimulation of type 1 cytokine production by bone marrow-derived B7-1 (and B7-2)-positive dendritic cells.
Gorczynski L; Chen Z; Hu J; Kai Y; Lei J; Ramakrishna V; Gorczynski RM
Transplant Research Division, Toronto Hospital, Ontario, Canada.
Journal of immunology (UNITED STATES) Jan 15 1999, 162 (2) p774-81, ISSN 0022-1767 Journal Code: IFB
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
We reported that hepatic mononuclear, nonparenchymal cells (NPC) can inhibit the immune response seen when allogeneic C57BL/6 dendritic cells (DC) are incubated with C3H spleen responder cells. Cells derived from these cultures transfer increased survival of C57BL/6 renal allografts in C3H mice. We also found that increased expression of OX-2 on DC was associated with inhibition of cytokine production and renal allograft rejection. We explored whether inhibition by hepatic NPC was a function of OX-2 expression by these cells. Fresh C57BL/6 spleen-derived DC were cultured with C3H spleen responder cells and other putative coregulatory cells. The latter were derived from fresh C3H or C57BL/6 liver NPC, or from C3H or C57BL/6 mice treated for 10 days by i.v. infusion of human Flt3 ligand. Different populations of murine bone marrow-derived DC from cultures of bone marrow with IL-4 plus granulocyte-macrophage-CSF were also used as a source of putative regulator cells. Supernatants of all stimulated cultures were examined for functional expression of different cytokines (IL-2, IL-4, IFN-gamma, and TGFbeta). We found that fresh C57BL/6 splenic DC induced IL-2, not IL-4, production. Cells from the sources indicated inhibited IL-2 and IFN-gamma production and promoted IL-4 and TGFbeta production. Inhibition was associated with increased expression of OX-2 on these cells, as defined by semiquantitative PCR and FACS analysis. By size fractionation, cells expressing OX-2 were a subpopulation of NLDC145+ cells. Our data imply a role for cells expressing OX-2 in the regulation of induction of cytokine production by conventional allostimulatory DC.
Record Date Created: 19990208

3/7/20 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09110556 97131836 PMID: 8977310
Effect of CD80 and CD86 blockade and anti-interleukin-12 treatment on mouse acute graft-versus-host disease.
Saito K; Yagita H; Hashimoto H; Okumura K; Azuma M
Department of Immunology, Juntendo University School of Medicine, Tokyo, Japan.
European journal of immunology (GERMANY) Dec 1996, 26 (12) p3098-106, ISSN 0014-2980 Journal Code: EN5
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
We investigated the efficacy of a combination of anti-CD80 and **CD86** (CD80 + 86) monoclonal **antibodies** (mAb), anti-interleukin (IL)-12 mAb, or both, for prophylaxis in a mouse acute graft-versus-host-disease (GVHD) model. The treatment with a combination of anti-CD80 + 86 mAb

efficiently reduced the lethality of GVHD, whereas mAb against either CD80 or CD86 alone had an effect. A delay in lymphocyte reconstitution and GVHD-associated histological changes in organs was observed at 30 days post-bone marrow transplantation (BMT) even in the anti-CD80 + 86 mAb-treated mice, although these manifestations were resolved by 100 days. In vitro, host alloantigen-specific T cell proliferative responses and generation of CTL were significantly reduced by anti-CD80 + 86 treatment. Furthermore, anti-CD80 + 86 mAb preferentially inhibited the production of interferon (IFN)-gamma, but not IL-4 and IL-10, when cultures were assayed at 21 days. Although the anti-IL-12 mAb treatment alone inhibited the generation of cytotoxic T lymphocytes and IFN-gamma production in vitro, administration of anti-IL-12 mAb in vivo reversed the beneficial effects of anti-CD80 + 86 treatment on host survival post-BMT. The adverse effect of anti-IL-12 treatment seems to result from impairment of natural immunity and hematopoiesis, rather than as a consequence of an incomplete blockade of T helper (Th)1 responses. Our results suggest that the prevention of GVHD-induced death results from the efficient blockade of Th1 cell activation by the anti-CD80 + 86 treatment. However, further treatment is required for a complete prevention of GVHD, which seems to be partly mediated by Th2 cells.

Record Date Created: 19970204

3/7/21 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09043742 97025429 PMID: 8871619

Infusion of anti-B7.1 (CD80) and anti-**B7.2** (**CD86**) monoclonal **antibodies** **inhibits** murine **graft**-versus-host disease lethality in part via direct effects on CD4+ and CD8+ T cells.

Blazar BR; Sharpe AH; Taylor PA; Panoskaltsis-Mortari A; Gray GS; Korngold R; Vallera DA

Department of Pediatrics, University of Minnesota, Minneapolis 55455, USA.

Journal of immunology (UNITED STATES) Oct 15 1996, 157 (8) p3250-9, ISSN 0022-1767 Journal Code: IFB

Contract/Grant No.: P01-AI35296, AI, NIAID; R01 HL56076, HL, NHLBI; R01-AI34495, AI, NIAID; +

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

Efficient T cell proliferation requires costimulation via CD28/B7 or other pathways. Graft-vs-host disease (GVHD) is caused by activated donor T cells. We have found that the infusion of anti-B7.1 (CD80) + anti-B7.2 (CD86) mAb is effective in eliminating GVHD lethality induced by either CD8+ or CD4+ T cells. Donor CD4+ and CD8+ T cell expansion was **inhibited** by almost 100-fold as measured by enumerating thoracic duct lymphocytes (TDL) obtained early post-**transplant** . TDL retained anti-host responsiveness indicating that not all T cells were anergic. Although anti-CD80 or anti-CD86 mAb individually were ineffective in preventing CD8+ T cell GVHD lethality, each mAb was partially effective in CD4+ T cell-mediated GVHD. Because CD80 expression was found to be up-regulated on donor CD4+ TDL post-transplant, the GVHD capacity of donor CD4+ T cells deficient in CD80 was tested and found to be reduced similarly to that seen with anti-CD80 mAb. These studies demonstrate that anti-CD80 + anti-CD86 mAb infusion is effective in preventing GVHD lethality by inhibiting donor CD4+ or CD8+ T cell expansion and provide the first evidence that CD80 expression on donor T cells is critical for optimal GVHD lethality.

Record Date Created: 19961217

3/7/22 (Item 1 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

135240937 CA: 135(17)240937k PATENT
Use of a combination of agents that modulate B7 activity in inhibiting intestinal allograft rejection
INVENTOR(AUTHOR): Collins, Mary; Newell, Kenneth
LOCATION: USA
ASSIGNEE: Genetics Institute, Inc.
PATENT: PCT International ; WO 200168132 A1 DATE: 20010920
APPLICATION: WO 2001US8015 (20010313) *US PV189165 (20000314)
PAGES: 56 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: A61K-039/395A; A61K-031/445B; A61P-037/06B; A61K-039/395B; A61K-031/445B
DESIGNATED COUNTRIES: AE; AG; AL; AM; AT; AU; AZ; BA; BB; BG; BR; BY; BZ; CA; CH; CN; CO; CR; CU; CZ; DE; DK; DM; DZ; EE; ES; FI; GB; GD; GE; GH; GM; HR; HU; ID; IL; IN; IS; JP; KE; KG; KP; KR; KZ; LC; LK; LR; LS; LT; LU; LV; MA; MD; MG; MK; MN; MW; MX; MZ; NO; NZ; PL; PT; RO; RU; SD; SE; SG; SI; SK; SL; TJ; TM; TR; TT; TZ; UA; UG; UZ; VN; YU; ZA; ZW; AM; AZ; BY; KG; KZ; MD; RU; TJ; TM DESIGNATED REGIONAL: GH; GM; KE; LS; MW; MZ; SD; SL; SZ; TZ; UG ; ZW; AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE; TR; BF; BJ; CF; CG; CI; CM; GA; GN; GW; ML; MR; NE; SN; TD; TG
SECTION:
CA215010 Immunochemistry
CA201XXX Pharmacology
IDENTIFIERS: intestinal allograft survival B7 antibody rapamycin
DESCRIPTORS:
Transplant and Transplantation...
allotransplant, small intestine; use of antibodies to B7-1 and B7-2 and a rapamycin compd. in inhibiting intestinal allograft rejection
Chemokine receptors...
.beta. chemokine receptor CCR5; inhibiting cytokine prodn. and the CD28/B7 pathway by anti-B7 antibodies in relation to inhibiting intestinal allograft rejection
Interferons...
.gamma.; inhibiting cytokine prodn. and the CD28/B7 pathway by anti-B7 antibodies in relation to inhibiting intestinal allograft rejection
CD28(antigen)... Interleukin 12... Interleukin 2... RANTES(chemokine)...
Tumor necrosis factors...
inhibiting cytokine prodn. and the CD28/B7 pathway by anti-B7 antibodies in relation to inhibiting intestinal allograft rejection
Chemokines...
macrophage inflammatory protein 1; inhibiting cytokine prodn. and the CD28/B7 pathway by anti-B7 antibodies in relation to inhibiting intestinal allograft rejection
Antibodies...
monoclonal; use of antibodies to B7-1 and B7-2 and a rapamycin compd. in inhibiting intestinal allograft rejection
Intestine...
small, allotransplant; use of antibodies to B7-1 and B7-2 and a rapamycin compd. in inhibiting intestinal allograft rejection
Antibodies... CD80(antigen)... CD86(antigen)... Immunosuppression...
Immunotherapy... Signal transduction,biological...
use of antibodies to B7-1 and B7-2 and a rapamycin compd. in inhibiting intestinal allograft rejection
CAS REGISTRY NUMBERS:
53123-88-9D derivs., use of antibodies to B7-1 and B7-2 and a rapamycin compd. in inhibiting intestinal allograft rejection
53123-88-9 use of antibodies to B7-1 and B7-2 and a rapamycin compd. in inhibiting intestinal allograft rejection

3/7/23 (Item 2 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

133295356   CA: 133(21)295356j   PATENT
Fusion proteins of novel CTLA4/CD28 ligands and uses therefore
INVENTOR(AUTHOR): Freeman, Gordon J.; Nadler, Lee M.; Gray, Gary S.; Greenfield, Edward
LOCATION: USA
ASSIGNEE: Dana Farber Cancer Institute; Replingen Corporation
PATENT: United States ; US 6130316 A DATE: 20001010
APPLICATION: US 280757 (19940726) *US 101624 (19930726) *US 109393 (19930819) *US 147773 (19931103)
PAGES: 83 pp., Cont.-in-part of U.S. Ser. No. 109,393, abandoned.
CODEN: USXXAM LANGUAGE: English CLASS: 530350000; C07K-019/00A; C07K-014/705B; C07H-021/00B
SECTION:
CA215002 Immunochemistry
CA201XXX Pharmacology
CA203XXX Biochemical Genetics
CA263XXX Pharmaceuticals
IDENTIFIERS: B7 antigen Ig fusion protein gene, T cell immunol disease immunosuppressant immunostimulant, CTLA4 CD28 ligand Ig fusion protein
DESCRIPTORS:
T cell(lymphocyte)...
    activation, costimulator; fusion proteins of novel CTLA4/CD28 ligands or B7-2 antigen for enhancing or suppressing T cell-mediated immune response
Complement...
    activation; fusion proteins of novel CTLA4/CD28 ligands or B7-2 antigen for enhancing or suppressing T cell-mediated immune response
Antigen-presenting cell... Astrocyte... B cell(lymphocyte)... Dendritic cell... Fibroblast... Monocyte... Oligodendrocyte...
    antigen; fusion proteins of novel CTLA4/CD28 ligands or B7-2 antigen for enhancing or suppressing T cell-mediated immune response
Transplant and Transplantation...
    bone marrow, allogenic; fusion proteins of novel CTLA4/CD28 ligands or B7-2 antigen for enhancing or suppressing T cell-mediated immune response
Antigens...
    B7-3; fusion proteins of novel CTLA4/CD28 ligands or B7-2 antigen for enhancing or suppressing T cell-mediated immune response
Drug delivery systems...
    carriers; fusion proteins of novel CTLA4/CD28 ligands or B7-2 antigen for enhancing or suppressing T cell-mediated immune response
Ligands...
    CTLA4/CD28; fusion proteins of novel CTLA4/CD28 ligands or B7-2 antigen for enhancing or suppressing T cell-mediated immune response
Mutation...
    deletion, identification; fusion proteins of novel CTLA4/CD28 ligands or B7-2 antigen for enhancing or suppressing T cell-mediated immune response
Blood vessel...
    endothelium, antigen; fusion proteins of novel CTLA4/CD28 ligands or B7-2 antigen for enhancing or suppressing T cell-mediated immune response
Immunoglobulins...
    fusion protein; fusion proteins of novel CTLA4/CD28 ligands or B7-2 antigen for enhancing or suppressing T cell-mediated immune response
Allergy... Animal tissue culture... Antigens... Autoimmune disease... Carcinoma... cDNA... cDNA sequences... CD80(antigen)... CD86(antigen)... Drug screening... Eukaryote(Eukaryotae)... Fusion proteins(chimeric proteins)... Gene therapy... Hybridoma... Immunostimulants... Immunosuppressants... Infection... Insect(Insecta)... Leukemia... Lymphocyte... Lymphoma... Melanoma... Molecular cloning... Neoplasm... Pathogen... Probes(nucleic acid)... Protein sequences... Sarcoma... Transplant rejection...
    fusion proteins of novel CTLA4/CD28 ligands or B7-2 antigen for

enhancing or suppressing T cell-mediated immune response
Transplant and Transplantation...
graft-vs.-host reaction; fusion proteins of novel CTLA4/CD28 ligands or B7-2 antigen for enhancing or suppressing T cell-mediated immune response
Mutation...
insertion, identification; fusion proteins of novel CTLA4/CD28 ligands or B7-2 antigen for enhancing or suppressing T cell-mediated immune response
Immunoglobulin receptors...
interaction; fusion proteins of novel CTLA4/CD28 ligands or B7-2 antigen for enhancing or suppressing T cell-mediated immune response
Eye...
keratocyte, antigen; fusion proteins of novel CTLA4/CD28 ligands or B7-2 antigen for enhancing or suppressing T cell-mediated immune response
Skin...
Langerhans' cell, antigen; fusion proteins of novel CTLA4/CD28 ligands or B7-2 antigen for enhancing or suppressing T cell-mediated immune response
CD28(antigen)... CTLA-4(antigen)...
ligand; fusion proteins of novel CTLA4/CD28 ligands or B7-2 antigen for enhancing or suppressing T cell-mediated immune response
Animal cell...
mammalian; fusion proteins of novel CTLA4/CD28 ligands or B7-2 antigen for enhancing or suppressing T cell-mediated immune response
Histocompatibility antigens...
MHC (major histocompatibility complex), class I; fusion proteins of novel CTLA4/CD28 ligands or B7-2 antigen for enhancing or suppressing T cell-mediated immune response
Histocompatibility antigens...
MHC (major histocompatibility complex), class II; fusion proteins of novel CTLA4/CD28 ligands or B7-2 antigen for enhancing or suppressing T cell-mediated immune response
Antibodies...
monoclonal; fusion proteins of novel CTLA4/CD28 ligands or B7-2 antigen for enhancing or suppressing T cell-mediated immune response
Nerve,neoplasm...
neuroblastoma; fusion proteins of novel CTLA4/CD28 ligands or B7-2 antigen for enhancing or suppressing T cell-mediated immune response
T cell(lymphocyte)...
proliferation; fusion proteins of novel CTLA4/CD28 ligands or B7-2 antigen for enhancing or suppressing T cell-mediated immune response
Mutation...
substitution, identification; fusion proteins of novel CTLA4/CD28 ligands or B7-2 antigen for enhancing or suppressing T cell-mediated immune response
Cell activation...
T cell, costimulator; fusion proteins of novel CTLA4/CD28 ligands or B7-2 antigen for enhancing or suppressing T cell-mediated immune response
Cell proliferation... Cytokines...
T cell; fusion proteins of novel CTLA4/CD28 ligands or B7-2 antigen for enhancing or suppressing T cell-mediated immune response
Immunity...
T cell-mediated; fusion proteins of novel CTLA4/CD28 ligands or B7-2 antigen for enhancing or suppressing T cell-mediated immune response
Bone marrow...
transplant, allogenic; fusion proteins of novel CTLA4/CD28 ligands or B7-2 antigen for enhancing or suppressing T cell-mediated immune response
CAS REGISTRY NUMBERS:
151285-69-7 152744-43-9 amino acid sequence; fusion proteins of novel CTLA4/CD28 ligands or B7-2 antigen for enhancing or suppressing T

cell-mediated immune response
162914-26-3 162952-69-4 nucleotide sequence; fusion proteins of novel CTLA4/CD28 ligands or B7-2 antigen for enhancing or suppressing T cell-mediated immune response
129405-59-0 171041-11-5 171041-12-6 281236-43-9 281236-44-0 281236-45-1 281236-46-2 281236-47-3 281236-48-4 281236-49-5 281236-50-8 281236-51-9 281236-52-0 281236-53-1 281236-54-2 281236-55-3 281236-56-4 281236-57-5 281236-58-6 281236-59-7 281236-60-0 281236-61-1 281236-62-2 281236-63-3 281236-64-4 281236-65-5 281236-66-6 281236-67-7 281236-68-8 281236-69-9 281236-72-4 281236-74-6 281236-76-8 281236-77-9 281236-78-0 281236-79-1 281236-80-4 281236-81-5 300756-19-8 300756-20-1 unclaimed nucleotide sequence; fusion proteins of novel CTLA4/CD28 ligands and uses therefore
148685-04-5 273716-40-8 281236-73-5 281236-75-7 unclaimed protein sequence; fusion proteins of novel CTLA4/CD28 ligands and uses therefore
162902-20-7 257280-30-1 280748-36-9 280748-37-0 unclaimed sequence; fusion proteins of novel CTLA4/CD28 ligands and uses therefore

3/7/24 (Item 3 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

130223295 CA: 130(17)223295d PATENT
Preparation of imidazoquinoxaline protein tyrosine kinase inhibitors
INVENTOR(AUTHOR): Barrish, Joel C.; Chen, Ping; Das, Jagabandhu; Iwanowicz, Edwin J.; Norris, Derek J.; Padmanabha, Ramesh; Roberge, Jacques Y.; Schieven, Gary L.
LOCATION: USA
ASSIGNEE: Bristol-Myers Squibb Company
PATENT: PCT International ; WO 9909845 A1 DATE: 19990304
APPLICATION: WO 98US16027 (19980803) *US 56770 (19970825) *US 69159 (19971209)
PAGES: 315 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: A31K-031/54A; A31K-031/495B; C07D-403/02B; C07D-413/14B DESIGNATED COUNTRIES: AL; AM; AT ; AU; AZ; BA; BB; BG; BR; BY; CA; CH; CN; CU; CZ; DE; DK; EE; ES; FI; GB; GE; GH; GM; HU; ID; IL; IS; JP; KE; KG; KP; KR; KZ; LC; LK; LR; LS; LT; LU; LV; MD; MG; MK; MN; MW; MX; NO; NZ; PL; PT; RO; RU; SD; SE; SG; SI; SK; SL; TJ; TM; TR; TT; UA; UG; UZ; VN; YU; ZW; AM; AZ; BY; KG; KZ; MD; RU; TJ; TM
DESIGNATED REGIONAL: GH; GM; KE; LS; MW; SD; SZ; UG; ZW; AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE; BF; BJ; CF; CG; CI; CM; GA; GN; GW; ML; MR; NE; SN; TD; TG
SECTION:
CA228017 Heterocyclic Compounds (More Than One Hetero Atom)
CA201XXX Pharmacology
IDENTIFIERS: imidazoquinoxaline prepn protein tyrosine kinase inhibitor
DESCRIPTORS:
Glycoproteins(specific proteins and subclasses)...
gp39, pharmaceutical compns. also contg. fusion proteins of; prepn. of imidazoquinoxalines as protein tyrosine kinase inhibitors
Tumor necrosis factor .alpha....
inhibitors, antibodies, or receptors; pharmaceutical compns. also contg.; prepn. of imidazoquinoxalines as protein tyrosine kinase inhibitors
Antibodies... Antiproliferative agents... Cytotoxic agents... Nonsteroidal anti-inflammatory drugs... Steroids,biological studies...
pharmaceutical compns. also contg.; prepn. of imidazoquinoxalines as protein tyrosine kinase inhibitors
CD40(antigen)...
pharmaceutical compns. also contg. fusion proteins of; prepn. of imidazoquinoxalines as protein tyrosine kinase inhibitors
CD2(antigen)... CD3(antigen)... CD4(antigen)... CD80(antigen)...

CD86(antigen)... Cell adhesion molecules... CTLA-4(antigen)... Interleukin 2 receptors...
pharmaceutical compns. contg. antibody to; prepn. of imidazoquinoxalines as protein tyrosine kinase inhibitors

Allergy inhibitors... Antiarthritics... Antiasthmatics... Antitumor agents ...
prepn. of imidazoquinoxalines as protein tyrosine kinase inhibitors

Tumor necrosis factor receptors...
sol.; pharmaceutical compns. also contg.; prepn. of imidazoquinoxalines as protein tyrosine kinase inhibitors

Allergic rhinitis... Atopic dermatitis... Autoimmune thyroiditis... Contact dermatitis... Graft vs. host reaction... Guillain-Barre syndrome... Hypersensitivity... Inflammatory bowel diseases... Ischemia... Lupus erythematosus... Multiple sclerosis... Psoriasis... Reperfusion injury... Transplant rejection...
treatment; prepn. of imidazoquinoxalines as protein tyrosine kinase inhibitors

CAS REGISTRY NUMBERS:
1196-57-2P 1790-91-6P 4784-02-5P 5344-97-8P 23309-16-2P 25652-34-0P
26286-54-4P 27841-33-4P 53525-65-8P 68008-32-2P 89898-96-4P
100379-00-8P 102186-93-6P 173416-54-1P 179042-26-3P 190198-52-8P
221025-36-1P 221025-37-2P 221025-38-3P 221067-97-6P 221067-99-8P
221068-01-5P 221068-03-7P 221068-05-9P 221068-08-2P 221068-10-6P
221068-13-9P 221068-15-1P 221068-27-5P 221068-29-7P 221068-40-2P
221068-42-4P 221068-47-9P 221068-51-5P 221068-53-7P 221068-55-9P
221068-58-2P 221068-60-6P 221068-62-8P 221068-64-0P 221068-66-2P
221068-69-5P 221068-72-0P 221068-74-2P 221068-76-4P 221068-78-6P
221068-80-0P 221068-82-2P 221068-84-4P 221068-86-6P 221068-88-8P
221068-90-2P 221068-92-4P intermediate; prepn. of imidazoquinoxalines as protein tyrosine kinase inhibitors
59865-13-3 104987-11-3 128794-94-5 140608-64-6 pharmaceutical compns. also contg.; prepn. of imidazoquinoxalines as protein tyrosine kinase inhibitors
80449-02-1 114051-78-4 140208-17-9 141349-87-3 141349-89-5 144941-32-2 145539-86-2 prepn. of imidazoquinoxalines as protein tyrosine kinase inhibitors
64-19-7 67-64-1 95-54-5 100-51-6 100-52-7 103-82-2 108-91-8 142-62-1 288-32-4 reactions, starting material; prepn. of imidazoquinoxalines as protein tyrosine kinase inhibitors
119138-29-3DP 221068-32-2DP 221068-34-4DP 221068-36-6DP 221068-38-8DP resin-bound, intermediate; prepn. of imidazoquinoxalines as protein tyrosine kinase inhibitors
18278-34-7D resin-bound, starting material; prepn. of imidazoquinoxalines as protein tyrosine kinase inhibitors
53123-88-9 sol.; pharmaceutical compns. also contg.; prepn. of imidazoquinoxalines as protein tyrosine kinase inhibitors
87-59-2 87-62-7 87-63-8 88-05-1 88-74-4 90-04-0 98-80-6 99-56-9
102-51-2 108-68-9 109-01-3 109-55-7 109-90-0 348-54-9 363-51-9
372-09-8 444-14-4 446-11-7 446-34-4 615-36-1 622-40-2 625-08-1
693-98-1 824-94-2 867-13-0 882-33-7 920-37-6 920-39-8 924-44-7
925-90-6 1003-98-1 1072-84-0 1493-27-2 1592-00-3 2038-03-1
2213-63-0 2393-23-9 2516-47-4 2544-06-1 2924-09-6 3240-94-6
4530-20-5 4584-46-7 4653-11-6 5720-07-0 10340-91-7 13154-24-0
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221069-27-8 221069-30-3 221069-33-6 221069-36-9 221069-39-2
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221067-77-2P 221067-79-4P 221067-81-8P 221067-83-0P 221067-85-2P
221067-87-4P 221067-89-6P 221067-91-0P 221067-93-2P target compd.;
prepn. of imidazoquinoxalines as protein tyrosine kinase inhibitors

3/7/25 (Item 4 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

129027008 CA: 129(3)27008c PATENT
Identification of unique binding interactions between certain antibodies and the human b7.1 and b7.2 co-stimulatory antigens
INVENTOR(AUTHOR): Anderson, Darrell R.; Hanna, Nabil; Brams, Peter
LOCATION: USA
ASSIGNEE: Idec Pharmaceuticals Corporation
PATENT: PCT International ; WO 9819706 A1 DATE: 19980514
APPLICATION: WO 97US19906 (19971029) *US 746361 (19961108)
PAGES: 87 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: A61K-039/395A; C07K-016/18B; C07K-016/28B DESIGNATED COUNTRIES: AL; AM; AT; AU; AZ; BA; BB; BG; BR; BY; CA; CH; CN; CU; CZ; DE; DK; EE; ES; FI; GB; GE; GH; HU; ID; IL; IS; JP; KE; KG; KP; KR; KZ; LC; LK; LR; LS; LT; LU; LV; MD; MG; MK; MN; MW; MX; NO; NZ; PL; PT; RO; RU; SD; SE; SG; SI; SK; SL; TJ; TM; TR; TT; UA; UG; UZ; VN; YU; ZW; AM; AZ; BY; KG; KZ; MD; RU; TJ; TM
DESIGNATED REGIONAL: GH; KE; LS; MW; SD; SZ; UG; ZW; AT; BE; CH; DE; DK; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE; BF; BJ; CF; CG; CI; CM; GA; GN; ML; MR; NE; SN; TD; TG
SECTION:
CA215003 Immunochemistry
CA203XXX Biochemical Genetics
IDENTIFIERS: monoclonal antibody antigen B7 CD80 CD87, immunosuppressant antibody antigen B7 autoimmune disease
DESCRIPTORS:

Mouse... Primate...
    chimeric antibody; humanized or primatized monoclonal antibodies or light and heavy chains for inhibiting antigen B7.1 or B7.2 and for use as immunosuppressant for treating autoimmune diseases
Allergies... Aplastic anemia... Autoimmune diseases... B cell lymphoma... B cell(lymphocyte)... cDNA sequences... CD28(antigen)... CD80(antigen)... CD86(antigen)... CTLA-4(antigen)... Graft vs. host reaction... Idiopathic thrombocytopenic purpura... Immunosuppressants... Infection... Inflammation ... Insulin dependent diabetes mellitus... Interleukin 2... Monoclonal antibodies... Multiple sclerosis... Protein sequences... Psoriasis... Rheumatoid arthritis... Systemic lupus erythematosus... T cell(lymphocyte) ...
    humanized or primatized monoclonal antibodies or light and heavy chains for inhibiting antigen B7.1 or B7.2 and for use as immunosuppressant for treating autoimmune diseases
Biliary tract diseases...
    inflammatory; humanized or primatized monoclonal antibodies or light and heavy chains for inhibiting antigen B7.1 or B7.2 and for use as immunosuppressant for treating autoimmune diseases
  CAS REGISTRY NUMBERS:
186271-56-7 186271-58-9 186271-60-3 186271-62-5 186271-64-7
    208065-43-4 amino acid sequence; humanized or primatized monoclonal antibodies or light and heavy chains for inhibiting antigen B7.1 or B7.2 and for use as immunosuppressant for treating autoimmune diseases
186271-55-6 186271-57-8 186271-59-0 186271-61-4 186271-63-6
    186271-65-8 nucleotide sequence; humanized or primatized monoclonal antibodies or light and heavy chains for inhibiting antigen B7.1 or B7.2 and for use as immunosuppressant for treating autoimmune diseases

3/7/26   (Item 5 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

125084636   CA: 125(7)84636x   PATENT
  Methods for inhibiting graft versus host disease in bone marrow transplantation
  INVENTOR(AUTHOR): Gribben, John G.; Nadler, Lee M.; Gray, Gary S.
  LOCATION: USA
  ASSIGNEE: Repligen Corporation; Dana-Farber Cancer Institute
  PATENT: PCT International ; WO 9614865 A1 DATE: 960523
  APPLICATION: WO 95US14774 (951109) *US 337960 (941110)
  PAGES: 42 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: A61K-039/00A; C07K-016/28B DESIGNATED COUNTRIES: AU; CA; JP DESIGNATED REGIONAL: AT; BE ; CH; DE; DK; ES; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE
  SECTION:
CA215001 Immunochemistry
  IDENTIFIERS: antibody B7 graft versus host disease, bone marrow transplant CTLA4 fusion protein
  DESCRIPTORS:
Antibodies... Antigens... Antigens,allo-... Antigens,B 7.2... Antigens,B7/BB-1... Antigens,CD28... Antigens,CTLA-4 (cytotoxic T-lymphocyte-activating, 4)... Bone marrow,transplant... Immunity... Immunoglobulins... Lymphocyte,T-cell... Proteins,specific or class, fusion products... Spleen,splenocyte... Transplant and Transplantation,graft-vs.-host reaction...
    inhibition of graft vs. host disease in bone marrow transplant with CTLA4Ig fusion protein and antibodies to B7-1 or B7-2 that suppress antigen-specific T cell responses
Blood corpuscle...
    peripheral; inhibition of graft vs. host disease in bone marrow transplant with CTLA4Ig fusion protein and antibodies to B7-1 or B7-2 that suppress antigen-specific T cell responses

3/7/27 (Item 6 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

122288908 CA: 122(23)288908k PATENT

Genes encoding B7-2 antigens that are CTL A4/CD 28 counter receptors involved in co-stimulation of T-cell activation and their uses

INVENTOR(AUTHOR): Freeman, Gordon J.; Nadler, Lee M.; Gray, Gary S.; Greenfield, Edward

LOCATION: USA

ASSIGNEE: Dana-Farber Cancer Institute; Repligen Corp.

PATENT: PCT International ; WO 9503408 A1 DATE: 950202

APPLICATION: WO 94US8423 (940726) *US 101624 (930726) *US 109393 (930819) *US 147773 (931103)

PAGES: 174 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: C12N-015/12A; C07K-014/705B; C07K-016/28B; C12N-005/10B; C12N-015/62B; A61K-035/12B; A61K-038/17B; A01K-067/027B; G01N-033/68B DESIGNATED COUNTRIES: AU; CA; JP

DESIGNATED REGIONAL: AT; BE; CH; DE; DK; ES; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE

SECTION:
CA215002 Immunochemistry
CA203XXX Biochemical Genetics

IDENTIFIERS: antigen B7 2 cDNA mouse human, T cell activation B7 2 antigen

DESCRIPTORS:

Antigens,CD28...
    antibodies to or fusion products with Igs, as immunosuppressants; genes encoding B7-2 antigens that are CTL A4/CD 28 counter receptors involved in T cell activation and their uses

Antigens...
    B7-1, in co-stimulation of